A Post Marketing Surveillance Study To Evaluate the Efficacy and Safety of Fixed Dose Amlodipine — Losartan Potassium for the Treatment of Hypertension in the Philippines

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Abstract

Background: This open label post marketing study was conducted to determine the efficacy and safety of a fixed dose combination of amlodipine - losartan in the treatment of hypertension in Filipino patients.

Methods: Eight hundred eighteen (818) male and female ambulatory patients aged 18-70 years with mild to moderate hypertension who were initially not responding to monotherapy were enrolled. Patients were prescribed (amlodipine 5mg - losartan potassium 50mg) as therapy. The primary end point was the change from baseline to sixth week in in both systolic and diastolic blood pressure. Details of any adverse event reported or noted during the treatment with the combination were recorded.

Results: There were 680 patients eligible for efficacy analysis. Mean age of patients was 53.36 ±11.3 years. One hundred twenty eight (15.6%) had dyslipidemia, 139 (16.9) had diabetes, while 7.7% had previously diagnosed cardiovascular disease. At baseline, patients had a mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 159 ± 18.3 mmHg and 96 ± 10.8 mmHg respectively. There was a statistically significant ($P < 0.001$) mean reduction of 30.87 ± 16.98 mmHg in SBP and 15.10 ± 10.68 mmHg in DBP at the end of follow up. By the 6th week 79.6% of patients achieved adequate SBP control of sat the while 76.6% had optimal diastolic BP. The differences in blood pressure were all statistically significant even when accounting for other comorbidities. Adverse events were noted in 2.9% with headache and peripheral edema being the most common side effects reported.

Conclusion: The results demonstrate that a fixed dose combination of amlodipine - losartan provides an effective and generally well-tolerated treatment option for hypertension in Filipino patients especially those with multiple cardiovascular risk factors who are unresponsive to monotherapy.

Keywords: hypertension, losartan, amlodipine

Introduction

Hypertension is one of the most preventable causes of cardiovascular diseases and premature death. It is a major risk factor for stroke, heart attack, heart failure, chronic kidney disease and cognitive decline.[1] Despite the widely accepted benefits of blood pressure reduction, the proportion of patients whose blood pressure is controlled is suboptimal. This is unacceptable since we know from various clinical trials that the majority of patients can achieve BP control with the use of effective antihypertensive medications.

The prevalence of hypertension in the Philippines has significantly increased from 22.5 percent in 2003 (which is not far from the Presyon 2 result of 21% prevalence rate) [2] to 25.3 percent in 2008 based on single BP determination according to the National Nutrition and Health Survey (NNHes II) which suggest that one in every four Filipino adults has hypertension or a BP reading equal to or higher than 140/90 mmHg. This poses not just a health problem but also an economic burden especially with the present economic situation.

The choice of antihypertensive agent is primarily directed by clinical guidelines and compelling indications such as high cardiovascular risk conditions like diabetes and chronic kidney disease. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[3] and European Society of Hypertension (ESH) guidelines,[4] therapy with more than one antihypertensive agent should be considered in patients with systolic blood pressure (SBP) more than 20 mmHg or diastolic blood pressure (DBP) more than 10 mmHg above goal. The decision for combined antihypertensive medications may also be considered when the patient experiences adverse effects of a single agent that may be improved by the addition of a second agent.

Several trials published have shown the better and greater benefit of combined therapy.[5] Combination therapy either by administration of two or more separate medications or fixed dose combinations is required in most patients with hypertension to achieve target goals. Fixed dose combinations can enhance adherence to medication regimens compared with treatment given

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as two separate agents. It also facilitates more prompt reduction in BP and better tolerability than higher-dose monotherapy, with the additional benefit of cost savings. There is evidence that better compliance leads to better blood pressure control.[6]

Objectives

To evaluate the safety and efficacy of amlodipine 5.0mg - losartan potassium 50mg for the treatment of mild to moderate hypertension.

Methodology

This was a six-week multicenter, nationwide, open label, non randomized, non comparative, prospective observational post marketing surveillance study which was designed and implemented in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines and approval from the local ethics committee (Ethics Review Board).

Study Population

Inclusion Criteria

1. Male and female ambulatory patients aged 18-70 years with mild to moderate hypertension (Stage 1 or 2 hypertension)
2. Patients not responding to monotherapy with calcium antagonists or angiotensin II receptor antagonists, for whom the treating doctor intended to prescribe TOZAM® (amlodipine 5mg - losartan potassium 50mg) as combination therapy

Exclusion Criteria

- Subjects with history of allergy or significant adverse reactions to the study drugs
- Pregnant women and lactating mothers
- Concurrent major illness or systemic dysfunction involving hepatic and renal system
- Concurrent therapy with medications that could affect blood pressure (Rifampin, Fluconazole and Indomethacin)
- Patients with congestive heart failure
- Patients suffering from angina
- Patients using potassium-sparing diuretics, potassium supplements and/or potassium containing salt substitutes
- Patients undergoing major surgery or during anesthesia with agents that produce hypotension
- Patients suffering from unilateral or bilateral renal artery stenosis associated with increase serum creatinine or blood urea nitrogen (BUN).

Patients of either gender who fulfilled the inclusion criteria were enrolled in the trial. Informed written consent was obtained from the patients/guardians before any investigative procedure was initiated. Patients were prescribed with amlodipine - losartan potassium 5.0mg/50mg using the brand TOZAM® as per the investigator's judgment. The dose was one tablet per day was adjusted and titrated upwards depending on the clinical response. A starting dose of amlodipine 5.0mg and losartan potassium 50mg was initiated for patients with a strongly activated renin-angiotensin-aldosterone system (in particular renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) under medical supervision. Patients were followed up at 1st week, second week, third week , fourth week and sixth week via telephone call and clinic inquiry. Any changes in recorded blood pressure, as well as side effects were entered in the case record forms as assessment of improvement, tolerability and overall efficacy. At the end of six weeks, the patients continued medical treatment as per the decision of the investigator/primary physician.

Efficacy and Safety Endpoints

Effectiveness of the study drugs were determined on the basis of patient's clinical response. The evaluation criteria would be the achievement of targeted (normal or prehypertension) blood pressure (JNC 2003 Guidelines) at the end of therapy.

Patients were evaluated for tolerability assessment. Safety was assessed by the occurrence of adverse events/ reactions after each visit after which the investigator would make a global evaluation regarding efficacy and safety of the study drugs. The nature and severity of the adverse events reported whether related or not to the study medication were documented in the case report form.

Sample Size

To determine the drug's effect with a one in 1000 background incidence of an adverse reaction and an added incidence of one in 100 with 95% confidence interval (alpha of 0.05; 1-beta of 0.8) the sample size was estimated at 500 patients.[7]

Data Analysis

Quantitative data were described as a mean ±SD while qualitative data was reported in frequency and percent distribution. Paired t-test was applied to continuous data while nominal data was analyzed using Fisher exact test. McNemar test was used to determine the significance of change in the proportion of blood pressure control from baseline to the last observation period. A p value of less than 0.05 was considered statistically significant. All analyses were done using SPSS version 22.0 (2013).

Results

The study flowchart is shown in Figure 1 show that out of 1000 screened patients, there were 818 patients included at

baseline. The clinical demographics at the start of the study are shown in Table I. The mean age of patients was 53.36 ±11.3 years. The subjects were mostly females comprising 58.7%. The most common concomitant disease was diabetes mellitus (16.9%) followed by dyslipidemia (15.6%). Sixty-three (7.7%) patients were previously diagnosed with cardiovascular disease. The patients had a mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 159 ± 18.3 mmHg and 96 ± 10.8 mmHg respectively. The most common drugs taken by patients together with the trial medication were anti-diabetic and lipid lowering drugs for dyslipidemia.

Figure 1: Study flowchart

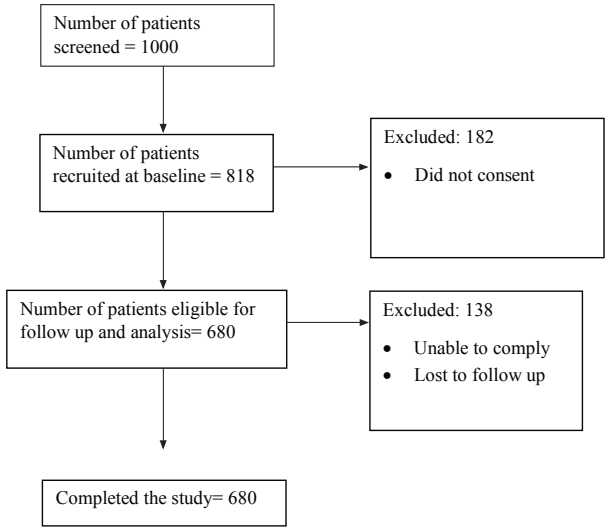

Table I. Baseline characteristics of patients at the start of the study (N=818)

Characteristic	(%) ± SD
Age	53.36 ±11.3
Male	338 (41.3)
Female	480 (58.7)
Co morbidities	
Prior CVD	63 (7.7)
Dyslipidemia	128 (15.6)
Diabetes	139 (16.9)
GI disease	14 (1.7)
Anemia	1 (0.7)
Genitourinary Disease	22 (2.8)
Vertigo	7 (0.6)
Respiratory	24 (2.9)
Vital signs	Mean ± SD
Baseline SBP	159 ± 18.3
Baseline DBP	96 ± 10.8

Efficacy Analysis

Out of the 818 patients, 138 patients were excluded either due to non compliance or loss to follow up. Six hundred eighty patients were eligible for efficacy analysis. There were significant decreases in mean blood pressures of patients from baseline to the end of the observation period (Table II).

Table II. Assessment of blood pressure of patients in the study

Blood pressure	Baseline		End Follow-up		Difference		p-value
	mean	sd	Mean	sd	mean	sd	
N= 680 patients							
Systolic BP (mmHg)	159	17.33	128	11.47	30.87	16.98	p< 0.001
Diastolic BP(mmHg)	96	10.23	81	7.76	15.10	10.68	p< 0.001

At the end of the follow up period (sixth week) the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased to 128 mmHg and 81 mmHg respectively. There was a mean change of 31±16.98 mmHg in SBP and 15±10.68 mmHg in DBP. All changes were statistically significant, even when accounting for risk factors such as concomitant cardiovascular disease, diabetes and dyslipidemia (p=<0.001) The assessment of blood pressure response to treatment is shown in Table III. At the start of the study, 37.4% of patients were classified with Stage 1 hypertension while 56.9% were Stage 2 based on systolic blood pressure. At the end of the follow up period, the frequency distribution of systolic hypertension decreased to 18.4% having Stage 1 and only 2.1% had Stage 2 (p< 0.001). There were 79.6% patients who achieved adequate control of systolic BP (<140 mmHg) at the last visit while 76.6% had adequate diastolic BP control (<90 mmHg)). Overall BP control (<140 mmHg systolic and <90 mmHg diastolic) achieved was 66.6%. There was a significant (P < 0.001) difference in the normalization status of BP (SBP, DBP and overall BP) at sixth week compared to baseline The achievement of adequate blood pressure control was also analyzed with regards to other co morbid conditions. Among patients with concomitant CVD, the overall control of hypertension was 75.9%. The diabetic group showed adequate control of blood pressure at the end of last visit at 71.9%. In the dyslipidemia group, 74.4% achieved adequate control. All the changes were also statistically significant. (p<0.001)

Safety Results

The summary of adverse events is summarized in Table IV. Adverse effects were reported by 24 patients (2.9%) The most frequent events were headache (six patients) and edema (five patients) Among the three patients where amlodipine was the suspected drug, one had both edema and dizziness while two had edema alone. In patients in whom the suspected drug was not indicated, the most common event was headache. Most of the events were mild in severity while two cases of headache and one case of numbness were classified as severe.

Table III. Assessment of blood pressure response of patients to treatment (N=680)

Response	Baseline		End Follow-up		P-value
	No.	%	No.	%	
Systolic BP					
Normal (<120mmHg)	1	0.1	73	10.7	*p*< 0.001
Pre-Hypertensive (120-139 mmHg)	38	5.6	468	68.8	
Stage I Hypertensive (140-159 mmHg)	254	37.4	125	18.4	
Stage II Hypertensive (≥160 mmHg)	387	56.9	14	2.1	
Controlled (<140 mmHg)	39	5.7	541	79.6	*p*< 0.001
Uncontrolled (≥140 mmHg)	641	94.3	139	20.4	
Diastolic BP					
Normal (<80 mmHg)	17	2.5	132	19.4	*p*< 0.001
Pre-Hypertensive (80-89 mmHg)	66	9.7	389	57.2	
Stage I Hypertensive (90-99 mmHg)	222	32.6	140	20.6	
Stage II Hypertensive (≥100 mmHg)	375	55.1	19	2.8	
Total					
Controlled (<90 mmHg)	83	12.2	521	76.6	*p*< 0.001
Uncontrolled (≥90 mmHg)	597	87.8	159	23.4	
Blood Pressure					
Controlled (SBP<140 mmHg & DBP<90 mmHg)	0	0.0	453	66.6	*p*< 0.001
Uncontroll	68	100.	227	33.4	

Table IV. Adverse events experienced by patients (n=818)

Adverse Events	No.	%
Specific Adverse Events	24	2.9
Body malaise	1	0.1
Cough	1	0.1
Dizziness	2	0.2
Edema	5	0.6
Headache	6	0.7
Lightheadedness	1	0.1
Nape pain	1	0.1
Nausea	1	0.1
Numbness / pain of extremities	2	0.2
Palpitation	2	0.2
Vertigo	1	0.1

Discussion

The goal of hypertensive therapy is aimed at reducing elevated blood pressure to optimal levels in order to reduce associated morbidity and mortality with minimal or no adverse events that affect quality of life. The results of this study shows that the combination of amlodipine and losartan is effective in reducing blood pressure to target levels in all indicated populations. This fixed drug combination has already been proven to be efficacious in other populations as well.[8] Many trials have shown that crossover monotherapy is only associated with a 40% rate of BP normalization.[9] For this reason, most guidelines are agreeing that majority of patients need combination therapy and are now more frequently recommended.[10] In our study, the use of amlodipine - losartan potassium 5.0mg/50mg allowed for statistically significant decreases in both systolic blood pressure as well as attainment of a adequate control of blood pressure by the sixth week of treatment in 67% of the study group. The fixed dose drug combination of amlodipine - losartan was generally well tolerated by the study population. Headache was the most common side effect seen in six patients followed by peripheral edema (five patients), which is expected with amlodipine therapy. The frequency of adverse events is low at 2.9% The drug combination of losartan - amlodipine are synergistic not only in terms of its mechanism of action on blood pressure lowering but also its tolerability profile. They can enhance and exert protective effects on target organs and minimize adverse effects by their antagonizing action.[11] Amlodipine being a dihydropyridine calcium channel blocker reduces arteriolar resistance. losartan, an angiotensin receptor blocker attenuates the pressor effect of angiotensin and also maintains Na+ and K+ balance. The increased hydrostatic pressure leading to increased transudation of fluid into the interstitial space by amlodipine may be attenuated by losartan owing to its effect in dilating efferent vascular bed. This dual and multiple mechanistic process is important in clinical practice not only to improve efficacy but tolerability as well.[12]

One of the reasons for not achieving hypertension control in patients is failure to adhere to the treatment regimen. Many patients who are on multi-drug therapy have low adherence as they tend to be more irregular with their daily intake of medications.[13] Fixed dose drug combination of anti hypertensive decrease the non compliance rate.[14] Indeed in our study which had an 83.1% compliance rate, optimal systolic blood pressure was achieved in 79.6% while 76.6% achieved adequate diastolic blood pressure in six weeks. Combining agents with complementary mechanisms produces greater blood pressure lowering effects than drugs with a single mechanism of action while acting together as well to decrease the occurrence of side effects,[15] which can also lead to improved compliance. This advantage is also evident regardless of the patient's risk factor profile, as this combination may represent the most applicable combination therapy for most hypertensive patients including added risk patients such as patients with chronic kidney disease (CKD) coronary artery disease (CAD), type 2 diabetes, obesity or metabolic syndrome.[16] Finally, there is evidence that this combination is also relatively cost

effective,[17] but other studies done in our local setting should be carried out for further information.

The combination therapy with the use of amlodipine-losartan on a fixed dose or single pill combination drug has been reported in other trials to effectively reduce BP and achieve high goal rates, without sacrificing tolerability.[18] This open label study without any comparator supports this finding. However, we recommend long-term comparative studies to verify its effects on target organs and also in a larger possibly multi ethnic population. This combination is associated with a better response rate with early control of BP, as well as better treatment compliance and can be used in the management of hypertension especially those patients who are non responding to monotherapy. This study adds data that support the recommendation that in patients who do not achieve recommended blood pressure reductions with a low dose of an antihypertensive agent, a combination therapy may be more effective than increasing the dose of a single agent.[19]

Conclusion

Amlodipine 5.0mg - losartan 50mg in a fixed-dose, single pill combination is an effective, safe and convenient treatment strategy in the management of hypertension especially those whose blood pressure targets are not achieved with monotherapy. Its efficacy extends among a wide range of patient populations and adds to the physician's armamentarium in attaining optimal blood pressure goals.

Disclosure

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