Research & Reviews: Journal of Pharmaceutical Analysis e-ISSN: 2320-0812

Efficacy of Allisartan Isoproxil in the Treatment of Mild-to-Moderate Essential Hypertension

Hongyi Wang, Yang Xi, Yuanyuan Chen, Luyan Wang, Fan Yang, Xining Lu, Ningling Sun*

Department of Hypertension, Peking University People's Hospital, Beijing, China

Research Article

Received: 15-Feb-2023, Manuscript No. JPA-23- 90462; **Editor assigned:** 17- Feb-2023, PreQC No. JPA-23- 90462 (PQ); **Reviewed:** 03-Mar-2023, QC No. JPA-23- 90462; **Revised:** 10-Mar-2023, Manuscript No. JPA-23-90462 (R); **Published:** 17-Mar -2023, DOI: 10.4172/2320-0812.12.1.005

***For Correspondence:**
Ningling Sun, Department of Hypertension, Peking University People's Hospital, Beijing, China
Email: sunnl@263.net

Citation: Wang H, et al. Efficacy of Allisartan Isoproxil in the Treatment of Mild-to-Moderate Essential Hypertension. RRJ Pharm Anal. 2023;12:005.

ABSTRACT

Objective: This study aimed to assess the clinical efficacy of allisartan isoproxil, a selective nonpeptide Angiotensin II (AT1) receptor blocker developed independently in China for the treatment of mild-to-moderate essential hypertension.

Methods: Patients with Essential Hypertension (EH) aged 18-75 years with 18.5 kg/m^2 ≤ BMI ≤ 30 kg/m^2, 140 mmHg ≤ Systolic Blood Pressure (SBP) <180 mmHg, and 90 mmHg ≤ Diastolic Blood Pressure (DBP)<110 mmHg were selected at 44 sites in China from September 9, 2016, to December 7, 2018. The individuals were administered 240 mg allisartan isoproxil tablets daily for 4 weeks, and those with controlled blood pressure continued monotherapy for 8 weeks. Patients with uncontrolled blood pressure were randomly assigned (1:1) to one of two groups: allisartan isoproxil tablet (240 mg)+indapamide sustained-release tablet (1.5 mg) (A+D) or allisartan isoproxil tablet+amlodipine besylate tablet (5 mg) (A+C) and were treated for 8 weeks. The primary efficacy endpoint was the sitting blood pressure control rate at week 12. The secondary efficacy endpoints were the rates of sitting blood pressure control, sitting blood pressure drop from baseline, and ambulatory blood pressure decrease at weeks 4 and 8.

Results: This study included 2126 patients. After 12 weeks of treatment, SBP and DBP decreased by 19.24 ± 12.02 and 10.63 ± 8.89 mmHg, respectively, and the overall rate of blood pressure control was 78.56%. After 4 and 8 weeks of treatment, the control rates were 68.85% and 79.99%, respectively.

Patients with controlled blood pressures after 4 weeks of treatment with allisartan isoproxil continued monotherapy, and Sitting Blood Pressures (SBP/DBP) decreased by 19.12 ± 11.71/10.84 ± 8.73 mmHg after 12 weeks of treatment (both p<0.0001). After 4 and 8 weeks of combination therapy, blood pressure was further reduced, and the reductions and rates of control were comparable between the A+D and A+C groups, with no statistically significant differences. A total of 48 patients with monotherapy-controlled blood pressure underwent ambulatory blood pressure monitoring, with a baseline 24 h ambulatory blood pressure of 133.29 ± 11.56/80.46 ± 10.19 mmHg, a mean decrease in ambulatory blood pressure of 10.04 ± 10.87/5.50 ± 8.07 mmHg after 12 weeks of treatment, and consistent reductions between day and night. SBP and DBP had trough-to-peak ratios of 64.64% and 62.63% and smoothness indices of 3.82 and 2.92, respectively. The overall rate of adverse reactions was 7.26%, with 96.15% mild and no severe or life-threatening adverse reactions.

Conclusion: An allisartan-isoproxil-based antihypertensive regimen that is safe and tolerable can effectively control blood pressure in patients with mild-to-moderate essential hypertension.

Keywords: Allisartan isoproxil; Essential hypertension; Efficacy; Safety

INTRODUCTION

Allisartan isoproxil tablet, a novel selective nonpeptide Angiotensin II type 1 (AT1) Receptor Blocker (ARB) independently developed in China, is a category 1.1 oral antihypertensive drug [1]. Allisartan isoproxil has been proven to reduce Blood Pressure (BP), protect organs, and have low toxicity in animal models [2]. Phase I clinical trial results revealed that allisartan isoproxil was safe and well-tolerated at daily doses ranging from 20 to 400 mg. A phase II multicenter, randomized, double-blind, a placebo-controlled clinical trial found that 240 mg of allisartan isoproxil daily was safe and effective in treating patients with mild-to-moderate Essential Hypertension (EH) [3]. A phase III multicenter, parallel-controlled, randomized, controlled clinical study showed that the antihypertensive efficacy and safety of 240 mg of allisartan isoproxil daily were not inferior to those of daily losartan potassium (50 mg) and that it could effectively and safely treat mild-to-moderate EH. This study aimed to assess the clinical efficacy and safety of allisartan isoproxil tablets for treating mild-to-moderate EH in a real-world clinical setting.

MATERIALS AND METHODS

Study subjects

The Institutional Review Boards (IRB) and Ethics Committees (EC) at each site reviewed and approved this multicenter, prospective, open-label post-marketing clinical study. Patients who met the inclusion criteria were selected from 44 study sites, including Peking University People's Hospital (ethics no.:2015 PHA043), between September 9, 2016, and December 7, 2018. Project Registration No.: CTR20160138 (Registration and Information Disclosure Platform for China Drug Clinical Studies, such as Hospital (Ethics No.:) Project Registration No.: Registration and Information Disclosure Platform for China Drug Clinical Studies.

Inclusion criteria: EH patients aged 18 to 75 years, with Body Mass Indices (BMI) of 18.5 kg/m^2 to 30 kg/m^2, sitting SBPs of 140 mmHg (1 mmHg=0.133 kPa) to <180 mmHg, and DBPs of 90 mmHg to 110 mmHg, and who signed

the Informed Consent Form (ICF). The concept of EH satisfies the criteria of the Chinese Guidelines for the Prevention and Treatment of Hypertension.

Exclusion criteria: Known or suspected secondary hypertension, atrial fibrillation, and malignant arrhythmia; a history of unstable coronary heart disease, systolic heart failure, or cerebrovascular accident within the past 6 months; diabetes mellitus with a fasting blood glucose ≥ 11 mmol/L; severe liver disease or hepatic insufficiency (ALT, AST or TBIL>2 times the upper limit of normal); chronic renal disease (eGFR<45 mL/min); known or suspected allergies to the study drugs; pregnant and breastfeeding women; and patients declared ineligible for clinical studies by the investigator.

Study drugs

Allisartan isoproxil tablets (240 mg/tablet), indapamide sustained-release tablets (1.5 mg/tablet), amlodipine besylate tablets (5 mg/tablet), and allisartan isoproxil placebo. Each drug was administered daily in the morning at a dose of one tablet/time/day. Shenzhen Salubris Pharmaceuticals Co., Ltd. provided all drugs.

Study methods

Drug treatment process: All patients received a 2-week placebo washout, and patients who met the inclusion criteria first received allisartan isoproxil monotherapy for 4 weeks only with controlled BP (SBP<140 mmHg and DBP<90 mmHg); they continued to receive allisartan isoproxil monotherapy for 8 weeks (12 weeks of treatment in total) only with uncontrolled BP; they were randomized at a ratio of 1:1 into the allisartan isoproxil 240 mg tablets+indapamide sustained-release 1.5 mg tablets group (A+D group) or the allisartan isoproxil tablets+amlodipine besylate 5 mg tablet group (A+C group) through the clinical trial remote Electronic Data Capture system (EDC) to receive treatment for 8 weeks (4 weeks of monotherapy and 8 weeks of combination therapy, for a total of 12 weeks).

BP measurement method: The subjects' sitting BPs in the clinic was measured using Omron 1300 automatic BP measuring equipment. The subjects rested quietly for at least 5 min in a sitting position, with their upper arms at the same level as their hearts. Then the measurements were repeated 2 min apart, averaging the three readings. For example, if there were differences of>10 mm Hg in SBP (including 10 mmHg) and differences of>5 mmHg in DBP in any of the three readings, two additional measurements had to be performed, with the mean of the three measurements being used after removing the maximum and minimum measurements (the mean value had to be rounded to an integer).

Ambulatory BP Monitoring (ABPM): This was an open-label study. ABPM was measured in 56 patients with hypertension before and after allisartan isoproxil treatment. Monitoring was performed using a 90201 ambulatory blood pressure (BP) meter from the US Space Laboratory. Baseline ABPM was performed 2 weeks after the placebo washout period, and post-treatment ABPM was performed the day before the end of the 12-week treatment period with allisartan isoproxil (240 mg/day). Measurements were taken every 20 min during the day (6 a.m. to 10 p.m.) and every 30 min during the evening (10 p.m. to 6 a.m.). At least one BP reading per hour was required, and the result was considered valid if accurate BP readings accounted for>80% of the total number of readings.

Evaluation variables

The rate of sitting BP control (control refers to sitting SBP/DBP<140/90 mmHg) and the change in sitting BP from baseline at weeks 4, 8, and 12 of treatment in the entire study population.

Change in sitting BP from baseline at weeks 4, 8, and 12 of allisartan isoproxil monotherapy and combination therapy.

Evaluation of BP by ABPM: (1) BP reduction before and after treatment; changes from baseline in SBP and DBP throughout the day, during the day, and at night. (2) To obtain the mean BP reduction per hour for all patients, the trough-to-peak ratio, BP reduction from baseline per hour for each patient, and mean were calculated. The peak value was the mean of the BP reductions at adjacent 2-hour time points of the maximum BP reduction within 2 to 8 h after administration, and the trough value was the mean BP reduction 2 h before the next administration [4,5]. The trough-to-peak ratio was calculated using the global approach, that is, the overall trough-to-peak ratio=mean trough/mean peak × 100%. (3) Smoothness index: The Smoothness Index (SI=mean/standard deviation of BP reduction per hour after treatment) was calculated using a global approach. The mean BP reduction per hour was calculated for all patients, followed by the SI according to the definition [6].

Safety assessment: The incidence of Adverse Events (AE) or Adverse Reactions (AR) refers to any unfavorable medical occurrence in patients or clinical study subjects following the administration of a drug. However, it does not necessarily have a causal relationship with the treatment. The relationship between AEs and the study drug was graded as follows: related, possibly related, doubtfully related, unrelated, and not evaluable. The first two were considered adverse reactions, the frequency of such reactions was recorded, and the occurrence and incidence of increase in relevant metabolic parameters were compared with baseline in various groups.

Compliance evaluation: If the subject's compliance was between 80% and 120%, compliance was assessed as good; if the compliance was <80% or >120%, compliance was assessed as poor.

Statistical analysis

All statistical tests were conducted using a two-sided test, with $P \leq 0.05$ considered statistically significant. Quantitative parameters such as the mean, Standard Deviation (SD), median, minimum, and maximum values were used to characterize the number of subjects. In addition, the number and percentage of subjects in each category were used to describe the categorical parameters.

According to the numerical characteristics of the variables, quantitative data such as age in the two groups were compared at baseline using the group t-test and Wilcoxon rank sum test, and categorical variables such as sex in the two groups were compared at baseline by the chi-square test or Fisher's exact test. SAS version 9.2 was used for all statistical analyses.

The Full Analysis Set (FAS) was used for efficacy analysis in this study by the ITT principle in the statistical analysis of drug clinical trials; that is, in the efficacy data analysis of this study, the patient data were included in the analysis as long as there was at least one primary efficacy evaluation after administration and no prohibited medications, to provide a relatively more objective response to the efficacy.

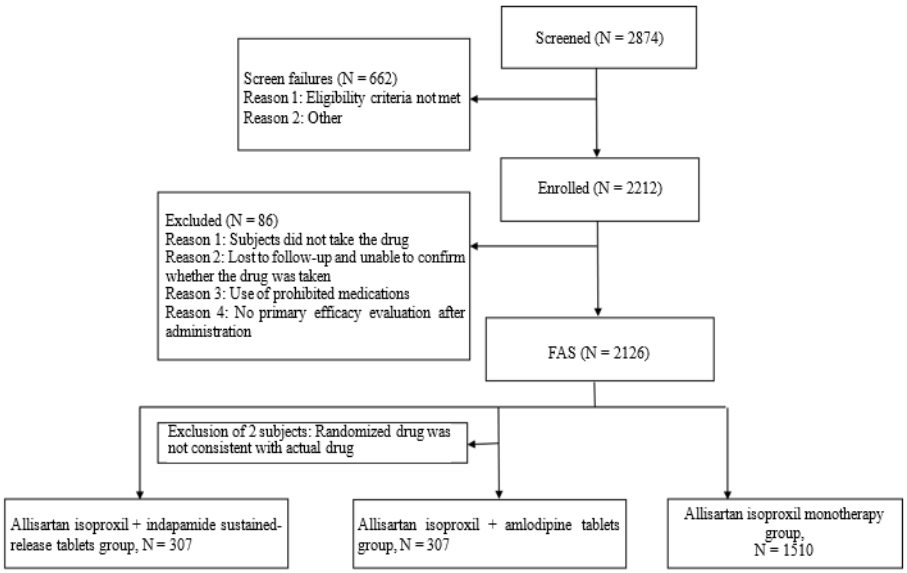
RESULTS

Patient screening

In this study, 2,874 patients were screened, 662 failed the screening, and 2,212 were enrolled. First, all subjects received allisartan monotherapy for 4 weeks. Then, patients with controlled BP received allisartan isoproxil 240 mg daily for 8 weeks, while those with uncontrolled BP were randomized at a ratio of 1:1 into one of two groups: allisartan isoproxil 240 mg+indapamide sustained-release 1.5 mg tablets daily for 8 weeks, or allisartan isoproxil 240 mg+amlodipine besylate 5 mg daily for 8 weeks. A total of 86 patients who did not take the drug could not be confirmed whether they had taken the drug, violated the eligibility criteria or lacked the primary efficacy evaluation

variables were eventually excluded, and 2126 patients with hypertension were eventually included in the efficacy evaluation. The screening procedure is illustrated in Figure 1.

Figure 1. Flow chart for subject screening.



Baseline characteristics

All enrolled patients had a mean age of 55.08 ± 10.18 years; 51.13% were male, 97.22% were Han, the mean BMI was 25.37 ± 2.55 kg/m^2, the mean duration of hypertension was 7.00 ± 7.26 years, and 71.12% had previously taken antihypertensive drugs. The differences in the baseline parameters between the two combination treatment groups were not statistically significant when the three groups were compared. In contrast, the monotherapy group had a lower baseline BP level, more females, lower BMIs, and a shorter duration of hypertension, Table 1 summarizes the basic characteristics of the patients.

Table 1. Baseline demographic and clinical characteristics (n=2,126).

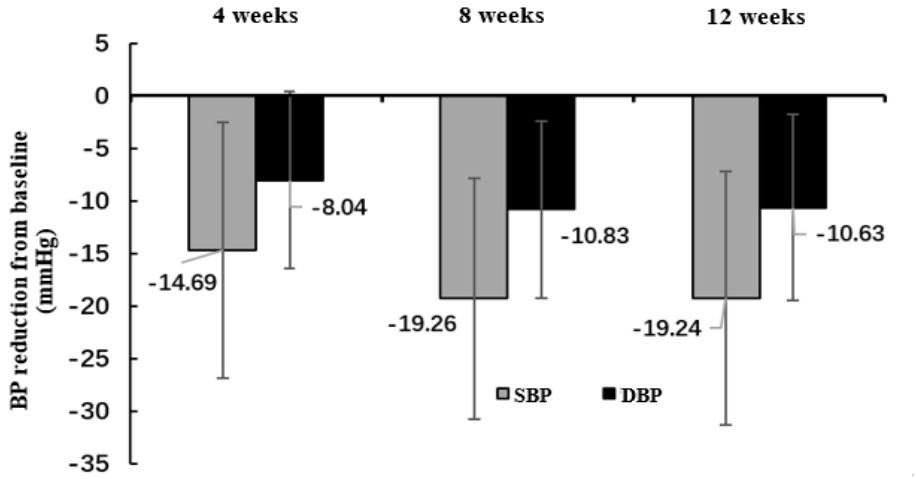
Clinical characteristics	Total (N=2126)	Monotherapy group (N=1510)	A+D group (N=307)	A+C group (N=307)	Pa	Pb
Age (y)	55.1 ± 10.2	55.0 ± 10.2	55.6 ± 9.6	54.9 ± 10.7	0.429	0.6442
Male (%)	1087(51.13%)	709(46.95%)	185(60.26%)	191(62.21%)	0.6192	<0.0001
BMI (kg/m^2)	25.37 ± 2.55	25.20 ± 2.56	25.77 ± 2.62	25.77 ± 2.36	0.9974	<0.0001
Sitting heart rate (bpm)	73.13 ± 8.84	72.81 ± 8.78	74.13 ± 9.47	73.63 ± 8.45	0.4862	0.0321
Sitting SBP* (mmHg)	149.61 ± 9.90	147.87 ± 9.19	153.90 ± 10.46	153.88 ± 10.15	0.9813	<0.0001
Sitting DBP* (mmHg)	92.01 ± 8.33	91.01 ± 7.76	94.49 ± 8.82	94.46 ± 9.49	0.9684	<0.0001
Course of hypertension (y)	7.00 ± 7.26	6.38 ± 6.86	8.96 ± 8.54	7.98 ± 7.31	0.1454	<0.0001
Prior medications	1512(71.12%)	1048(69.40%)	230(74.92%)	232(75.57%)	0.8517	0.0263

Note: *Baseline BP is the BP of patients when not taking the drug; BMI: Body Mass Index; A+D: allisartan isoproxil in combination with diuretics; A+C: allisartan isoproxil in combination with calcium antagonist; a: Comparison between the combination treatment groups; b: Comparison between the three treatment groups

Evaluation of overall BP reduction

The overall rate of sitting BP control in the three groups was 78.56% at week 12 of treatment. At weeks 4 and 8, the overall rates of sitting BP control were 68.85% and 79.99%, respectively. Figure 2 depicts the reductions from baseline in sitting SBP and DBP levels at weeks 4, 8, and 12 of treatment, and the differences were statistically significant (P<0.0001).

Figure 2. BP reductions from baseline in all subjects at weeks 4, 8, and 12 of treatment. **Note:** (▭) Systolic Blood Pressures (SBP); (■) Diastolic Blood Pressure (DBP).



Efficacy evaluation of allisartan isoproxil monotherapy

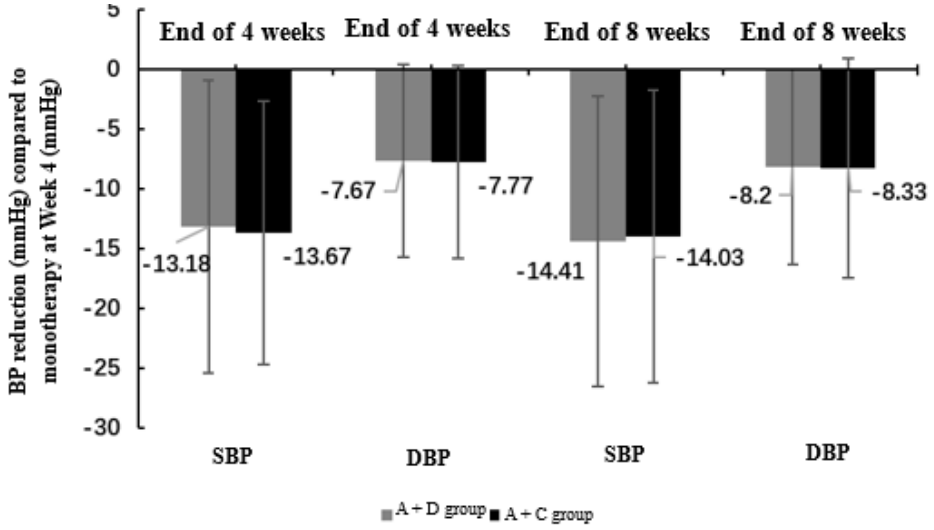
Patients treated with monotherapy had statistically significant reductions from baseline in sitting SBP of 18.59 ± 10.58 mmHg, 19.50 ± 11.05 mmHg, and 19.12 ± 11.71 mmHg, respectively (P<0.0001) at weeks 4, 8, and 12 of treatment, and reductions from baseline in sitting DBP of 10.59 ± 7.55 mmHg, 11.31 ± 8.13 mmHg, and 10.84 ± 8.73 mmHg, respectively (P<0.0001) at weeks 4, 8, and 12 of treatment.

Efficacy evaluation of combination therapies

At the end of the 4 weeks of monotherapy, 616 patients had uncontrolled BP, and two were excluded due to inconsistencies between the randomized drug and the actual drug. The remaining 614 patients were included in the efficacy analysis of combination treatment. After 8 weeks of continuous treatment, 307 patients in the allisartan isoproxil combined with the indapamide group had a BP control rate of 62.85%. After 8 weeks of continuous treatment, 307 patients in the allisartan isoproxil combined with the amlodipine group had a BP control rate of 57.68%.

There were no statistically significant differences in BP control rates between the two groups. Figure 3 depicts the difference in BP reductions between the two groups. The differences in BP reduction between the two groups and those at randomization (i.e., 4 weeks of monotherapy) were statistically significant (P<0.0001). There were no statistically significant differences in BP reductions between the two groups.

Figure 3. BP reductions in the two combination treatment groups after 4 weeks of monotherapy followed by 4 and 8 weeks of further treatment. **Note:** (■) A+D group; (■)A+C group.



ABPM results

In this study, 56 patients received ABPM before and after treatment with allisartan isoproxil monotherapy. Eight patients were excluded due to unqualified reporting of ABPM, and 48 were included in the efficacy evaluation. The study included 25 males and 23 females, with a mean age of 55.69 ± 12.90 years and a baseline BP of 140.04 ± 8.82/89.69 ± 7.37 mmHg.

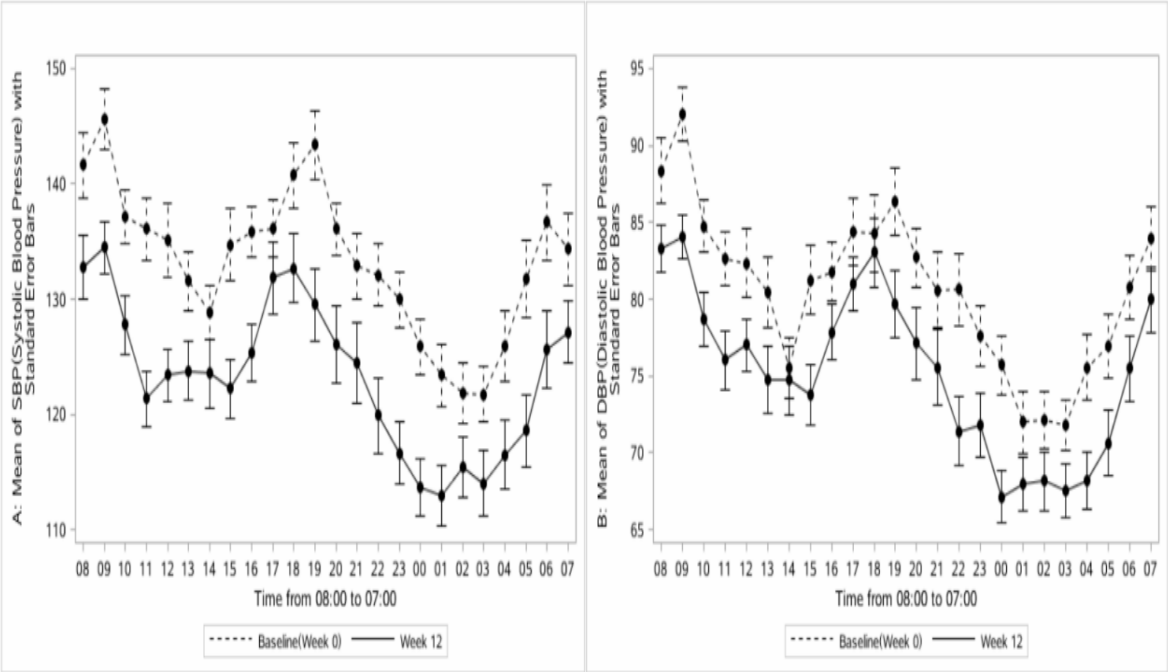
BP reduction: After 12 weeks of treatment with allisartan isoproxil monotherapy, the 24-hour, daytime, and nighttime BP decreased significantly and were statistically significant. In addition, SBP and DBP reductions were comparable across the periods (Table 2 and Figure 4).

Table 2. Ambulatory BP reduction after 12 weeks of allisartan isoproxil monotherapy.

Item	Baseline	12 weeks after treatment	Decrease (baseline-12 weeks)
Mean of 24 h values (mmHg)			
SBP	133.29 ± 11.56	123.25±12.29**	10.04 ± 10.87
DBP	80.46 ± 10.19	74.96±8.90**	5.50 ± 8.07
Mean of daytime values (mmHg)			
SBP	136.42 ± 11.66	126.48±13.26**	9.94 ± 13.14
DBP	83.10 ± 10.82	77.73±9.43**	5.38 ± 9.18
Mean of nighttime values (mmHg)			
SBP	127.35 ± 14.90	116.94±14.48**	10.42 ± 13.18
DBP	75.21 ± 10.58	69.77±9.76**	5.44 ± 9.22
Note: Compared to baseline **P<0.01			

Figure 4. Graph showing changes in 24 h ambulatory BP before and after treatment with allisartan isoproxil (mmHg).

Note: (---) Base line (Week 0); (—) Week 12.



Changes in BP rhythm: Thirty (62.5%) patients showed non-dippers or reverse-dippers on ABPM before treatment (< 10% reduction in nighttime and daytime BP), and only 33.33% of patients showed non-dippers or reverse-dippers after treatment (P=0.0010 by chi-square test). Sixteen patients (33.33%) reversed their non-dippers or reverse-dippers to normotensive rhythms.

Peak and trough of BP reduction: The peak value of SBP reduction was the mean of the reductions at 3 and 4 h after administration (14.17 mmHg), and the peak value of DBP reduction was the mean of the reductions at 2 and 3 h after administration (7.60 mmHg). SBP and DBP trough values were the means of the reductions 2 h before the next dose, which was 9.16 mmHg for SBP and 4.76 mmHg for DBP. After allisartan isoproxil treatment, the trough-to-peak ratios for SBP and DBP were 64.64% and 62.63%, respectively.

Smoothness index: The mean hourly reduction in SBP was 10.14 mmHg, and the standard deviation was 2.65 mmHg, resulting in an SBP smoothness index of 3.82. On the other hand, the mean hourly reduction in DBP was 5.44 mmHg, and the standard deviation was 1.86 mmHg, resulting in a smoothness index of 2.92 for DBP.

DISCUSSION

Allisartan isoproxil was the first selective nonpeptide ARB antihypertensive drug developed independently in China. It is metabolized by gastrointestinal esterase, which produces the active metabolite EXP 3174, also a product after losartan potassium metabolism in the liver. EXP 3174 can selectively bind to AT1 receptors with 1000 times the affinity to AT2 receptors, blocking the corresponding physiological effects of angiotensin II [1]. EXP3174 is widely distributed in the tissues, mainly in the liver, small intestine, large intestine, stomach, spleen, and lungs. Its concentration is considerably low in the brain tissue, indicating that the drug does not readily cross the blood-brain barrier. EXP3174 had a high plasma protein binding rate, with an average of 100% binding to rat plasma proteins

and 99.6% binding to human plasma proteins. As Allisartan isoproxil is not metabolized by hepatic enzymes, it has fewer drug interactions and is safer than losartan in combination therapy. EXP 3174 had a higher AUC than losartan (100 mg) after a single oral dose of 240 mg of allisartan isoproxil. A phase III clinical study of allisartan isoproxil compared the efficacy and safety of allisartan isoproxil 240 mg daily with losartan tablets 50 mg daily in treating mild to moderate EH, with 689 subjects randomly assigned to the allisartan isoproxil group or the losartan tablets group for 12 weeks of treatment. The results showed that allisartan isoproxil 240 mg tablets orally once daily reduced sitting BP by 14.9/9.1 mmHg after 12 weeks, which was non-inferior to losartan 50 mg (13.6/8.4 mmHg reduction in sitting BP). The antihypertensive effects in both groups were evident after 2 weeks of treatment. The most significant effect was achieved in week 4 of treatment, and the effect remained stable with the treatments lasting 8 and 12 weeks. Several small-sample studies in China have compared the efficacy and safety of allisartan isoproxil with valsartan, irbesartan, candesartan, and other drugs for treating EH, demonstrating the same antihypertensive effects and safety as the marketed angiotensin II receptors [7–12]. In this study, the 4-week BP control rate of allisartan isoproxil 240 mg monotherapy was 68.85%. The change from baseline in sitting BP was 14.69 ± 12.20/8.04 ± 8.41 mmHg, similar to the phase III clinical study of allisartan isoproxil results confirming the efficacy of BP reduction with allisartan isoproxil in the real world.

Hypertension is the most critical risk and predisposing factor for cardiovascular and cerebrovascular diseases. A 2015 survey shows that hypertension awareness, treatment, and control rates have significantly improved in China's population aged>18 years. However, the overall levels remain low at 51.6%, 45.8%, and 16.8%, respectively [13]. Combination therapy is required to achieve the target BP in patients with hypertension. RASI in combination with calcium antagonists (A+C) or diuretics (A+D) is the initial combination treatment regimen recommended by hypertension guidelines both at home and abroad [13-15]. RASI drugs can protect the heart and kidney by improving cardiac remodeling, decreasing renal hyperperfusion, and improving patients' long-term prognoses by inhibiting the renin-angiotensin system. However, the control rate of RASI monotherapy is limited, and combinations with calcium channel blockers or diuretics have shown the advantages of improving efficacy and reducing adverse reactions in terms of pharmacological mechanisms and clinical evidence. RASI can increase serum potassium slightly by reducing aldosterone secretion, counteracting hypokalemia induced by thiazide diuretics, and inhibiting the renin-angiotensin system, which is activated by decreased renal perfusion. Calcium antagonists dilate arteries and stimulate the sympathetic nervous system while lowering BP, which may activate the renin-angiotensin system. RASI dilates not only the arteries but also the veins; thus, its combination with calcium antagonists has synergistic antihypertensive effects and can reduce or counteract the side effects of dihydropyridine calcium antagonists, such as ankle edema. A study on avoiding cardiovascular events through combination therapies in patients living with systolic hypertension (ACCOMPLISH) showed that the control rates of high-risk hypertension treated with A+C and A+D single-tablet fixed combination therapies reached 75.4% and 72.4%, respectively, which were significant improvements compared to other treatment regimens at baseline [16]. Allisartan isoproxil is metabolized by gastrointestinal esterases to produce EXP 3174, an active metabolite that is not metabolized by liver enzymes and has few drug interactions, making it suitable for combination therapies. This study found that the combination treatment of allisartan isoproxil with indapamide or amlodipine for 8 weeks significantly reduced BP in subjects who's BP was not controlled after 4 weeks of allisartan isoproxil monotherapy. After 8 weeks of the combination treatment, the rates of BP control in the two groups were 62.85% and 57.68%, respectively, and the absolute values of BP reduction were (14.41 ± 12.12)/(8.20 ± 8.18) and (14.03 ± 12.24)/(8.33 ± 9.18) mmHg, respectively. The differences between the two groups were not statistically significant. The International Society of Hypertension (ISH) 2020 International Hypertension Practice

Guidelines recommend low-dose A+C as the initial treatment regimen for patients with general hypertension, which has sparked much debate in the academic community, and the superiority of A+C and A+D has also been widely discussed. Most experts now believe that the recommendations of the ISH guidelines are primarily based on their ease of application in countries and regions with varying economic levels. Most hypertension prevention and treatment guidelines at home and abroad recommend A+C or A+D as the best combination regimen. According to the findings of this study, both combinations can be chosen for simple BP reduction. Diuretics have the potential to cause metabolic abnormalities, whereas CCBs have no obvious contraindications, which may account for the increased use of A+C combination regimens in clinical practice. In addition, A+C may provide additional cardiovascular benefits; the ACCOMPLISH study showed a 20% reduction in the risk of the composite endpoint of cardiovascular-related death and cardiovascular events for A+C compared to A+D (0.80 [0.72 to 0.90], p<0.001).

Ambulatory Blood Pressure Monitoring (ABPM) is critical for reflecting daily BP patterns, mainly nocturnal BP. At the same time, ABPM has distinct advantages and is becoming increasingly crucial in reflecting the circadian rhythm of BP and the long-term effects and stability of antihypertensive drugs. Guidelines for hypertension are recommended, both at home and abroad. Reducing sodium intake, choosing 24-hour long-acting antihypertensive drugs, and taking antihypertensive drugs at bedtime are all strategies for controlling nighttime BP [17,18]. At the same time, clinicians have been concerned about controlling nighttime BP with drugs with different antihypertensive mechanisms. According to this study, a 12-week oral treatment with allisartan isoproxil once in the morning resulted in consistent daytime and nighttime BP reductions. After taking allisartan isoproxil, 33.3% of the patients with non-dipper BP at baseline reversed to dippers or overdippers. The mean nighttime BP in patients with overdippers after treatment was 100.55/64.82 mmHg, indicating that oral monotherapy administered in the morning can effectively reduce BP and correct abnormal BP rhythms without causing excessive reductions in nighttime BP. BP fluctuations frequently result in stroke and cardiovascular events during reduction. When evaluating an excellent antihypertensive drug, the 24-hour T/P ratio and smoothness index are frequently used to assess the long-term effects of drug treatment. Allisartan isoproxil was administered orally once in the morning in this study, and the T/P of both SBP and DBP was>60%, indicating that allisartan isoproxil had an antihypertensive effect that lasted for 24 h, had good long-term effects and stability, and could be administered once daily as a long-acting antihypertensive drug.

CONCLUSION

Allisartan isoproxil, a novel angiotensin II receptor blocker antihypertensive drug administered at a dose of 240 mg orally once daily, can effectively and safely treat mild-to-moderate essential hypertension and has good antihypertensive stability, particularly for nighttime blood pressure. In addition, the overall antihypertensive efficacy of allisartan isoproxil in combination with indapamide and allisartan isoproxil in combination with amlodipine was comparable, and combination therapy can be used as a reasonable option for patients whose BP is not controlled by allisartan isoproxil monotherapy. Generally, the higher the smoothness index, the more stable the BP reduction, and 24-hour stable BP control will aid in reducing cardiovascular and cerebrovascular event.

ACKNOWLEDGEMENTS

The following institutions and investigators are appreciated for their unwavering support during the conduct of the study (regardless of ranking): Sun Ningling (Peking University People's Hospital), Huo Yong (Peking University First Hospital), Liu Wei (Beijing Hospital), Ding Chunhua (Aerospace Center Hospital), Zhang Lixin (Beijing Luhe Hospital

Affiliated to Capital Medical University), Lv Shuzheng (Beijing Anzhen Hospital Affiliated to Capital Medical University), Dong Xichang (Dongying People's Hospital), Wang Yanfu (Affiliated Hospital of Jining Medical College), Jiang Lingyun (West China Hospital of Sichuan University), Dong Shaohong (Shenzhen People's Hospital), Gao Feng (Yanan University Affiliated Hospital), Wang Haichang (Tangdu Hospital of the Fourth Military Medical University of the People's Liberation Army), Li Xiaodong (Shengjing Hospital of China Medical University), Lin Hailong (Dalian Municipal Central Hospital), Chai Jianwen (People's Hospital of Zhengzhou), Yan Ji (Anhui Provincial Hospital), Ge Junbo (Zhongshan University), Chai Rui (Shihezi Hospital, Xinjiang Shihezi Hospital), Xu Xinjuan (First Affiliated Hospital of Xinjiang Medical University), Ning Zhongping (Shanghai Zhoupu Hospital), Zhao Mingzhong (Zhengzhou Ninth People's Hospital), Su Guohai (Jinan Central Hospital), Li Lipeng (Luoyang Third People's Hospital), Liu Huiliang (Chinese People's Armed Police Force Hospital), Qiu Chaohui (Tongren Hospital, Shanghai Jiaotong University School of Medicine), Li Yuhui (Guangdong Second Provincial General Hospital), Li Rong (The First Affiliated Hospital of Guangzhou University of Chinese Medicine), Lei Da (The First Affiliated Hospital of School of Clinical Medicine of Guangdong Pharmaceutical University), Zhang Fenfang (Yangquan First People's Hospital), Guo Renwei (Fenyang Hospital of Shanxi Province), Wang Shouli (Characteristic Medical Center of Strategic Support Force), Wei Haisong (PKUCare Lu'an Hospital), Zhang Xingwei (The Affiliated Hospital of Hangzhou Normal University), Li Jinqiao (Central Hospital of Zibo Mining Group Co., Ltd.), Wang Jun (Zibo Central Hospital), Wei Lin (Harbin First Hospital), Zhang Guochun (Harbin Second Hospital), Huang Rongjie (The First Affiliated Hospital of Guangxi Medical University), Chen Yongsheng (Fifth Affiliated Hospital of Zhengzhou University), Li Gongxin (Zhujiang Hospital of Southern Medical University), Liu Jinlai (The Third Affiliated Hospital of Zhongshan University), Zhang Shuyang (Peking Union Medical College Hospital of Chinese Academy of Medical Sciences), Wang Shuqing (The First Hospital of Qiqihar), Su Xi (Wuhan Asian Heart Hospital).

AUTHOR CONTRIBUTIONS

Professor Sun Ningling presided over the design of this study, participated in the study, and wrote the article. Professor Wang Hongyi participated in the design discussion of this study, participated in the study process, and wrote the full text. Ma Qingchun, Yang Fan, and Lu Xining participated in the implementation process of the study.

CONFLICTS OF INTEREST

The study expenses and drugs for this study were provided by Shenzhen Salubris Pharmaceuticals Co., Ltd. The authors did not participate in the company’s drug promotions or accept any unwarranted payments.

REFERENCES

1. Expert committee on rational use of drugs of the national health and family planning commission of prc. Guidelines for rational use of drugs of hypertension (2nd edition). Chinese Journal of the Frontiers of Medical Science (Electronic Version). 2017;9:28-126.
2. Wu MY, et al. Effects of allisartan, a new AT (1) receptor blocker, on blood pressure and end-organ damage in hypertensive animals. Acta Pharmacol Sin. 2009;30:307-313.
3. Li Y, et al. A randomized, double blind, placebo-controlled, multicenter phase II trial of allisartan isoproxil in essential hypertensive population at low-medium risk. PLoS One. 2015;10:e0117560.
4. Revision committee of guidelines for prevention and treatment of hypertension in china. Guidelines for prevention and treatment of hypertension in china 2010. Chinese Journal of Cardiology. 2011;39:579-616.
5. Wang H, al. Evaluation of antihypertensive efficacy of irbesartan and indapamide sustained-release tablets by

calculating trough-to-peak ratio and smoothness index via different methods. The Chinese Journal of Clinical Pharmacology. 2004;20:337-340.

6. Parati G, et al. The smoothness index: A new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. J Hypertens. 1998;16:1685-1691.
7. Zhang JQ, et al. Effects of allisartan isoproxil on blood pressure and target organ injury in patients with mild to moderate essential hypertension. Medicine (Baltimore). 2019;98:e14907.
8. Zhu Lixin, et al. Efficacy analysis of different drug regimens in the treatment of essential hypertension. Chronic Pathematology Journal. 2020;21:65-67.
9. Tang Yuyi, et al. Comparison of efficacy of allisartan isoproxil and valsartan in treatment of hypertension complicated with hyperuricemia. Journal of Hunan Normal University (Medical Sciences). 2020;17:40-42.
10. Wang Jun, et al. Observation on the curative effect of alisartan medoxomil in the treatment of elderly hypertension. Chin J Clin H. 2015;18:247-249.
11. Wu Yanting. Comparison of the application effect of candesartan and allisartan isoproxil in treatment of patients with essential hypertension. Harbin Medicine Journal. 2020;40:9-10.
12. Jing Shan, et al. Efficacy and safety of allisartan isoproxil in treatment of mild to moderate essential hypertension. Chin J Clin Pharmacol. 2013;29:728-731.
13. Revision committee of guidelines for prevention and treatment of hypertension in china. Guidelines for prevention and treatment of hypertension in china (2018 revision). Chin J Cardiol Med. 2019;24:24-56.
14. Williams B, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J, 2018; 39:3021-3104.
15. Unger T, et al. 2020 International society of hypertension global hypertension practice guidelines. J Hypertens. 2020;38:982-1004.
16. Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359:2417-2428.
17. Muntner P, et al. Measurement of blood pressure in humans: a scientific statement from the american heart association. Hypertens. 2019;73:e35-e66.
18. Bowles NP, et al. Chronotherapy for hypertension. Curr Hypertens Rep. 2018;20:97.