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Research Article

Antihypertensive Efficacy of Fimasartan and Additional Benefits in Patients with Renal Dysfunction

Antonio Méndez Durán[1]* and Julen Ocharán Corcuera[2]

[1]*Hospitals Division, Mexican Social Security Institute, USA*
[2]*Nephrology Service, Araba University Hospital- Santiago Apóstol, Spain*

Abstract

The Angiotensin Receptor Blockers (ARB) is the first-line antihypertensive drugs. The Fimasartan (FIMA), the last one of this family, has showed efficacy and antihypertensive security. Research objective is to identify the antihypertensive and antiproteinuric effect of Fimasartan on patients with type 2 Diabetes Mellitus (DB), High Blood Pressure (HBP) or Chronic Kidney Disease (CKD).

Material and methods: 24-Week Prospective Study (November 2014 – February 2015). Including subjects > 18 years old, CKD with RF > 30 mL/min or Albuminuria <500 mg/day; without severe or untreated hypertension, infectious of acute cardiac events. Those who discontinued the treatment, voluntary dropped out of the study, had an alteration of the TGF (>2 mL/month), increased serum creatinine >1 mg /month, or uncontrolled High Blood Pressure (FIMA's Dmax and addition of Thiazide Diuretic) were excluded.

BP target <130/80 and no <115/75 mm Hg. Variables: age, sex, TGF, determinations of urea in serum samples, creatinine, uric acid, albumin, calcium, phosphorus, hemoglobin, hematocrit and liver function; albuminuria. The percentage of patients who reached the antihypertensive objective with 60 and 120 mg/day and decreased albuminuria was estimated.

Results: 40 patients, 20 male and 20 female, 55,9 years old (mg: 30-74), 21 DM and 19 HBP. The Baseline Proteinuria 4, 8, 12, 16, 20 and 24 weeks were: 383, 355, 346, 280, 198, 210 and 201 (p >0,5); TFG 38,5, 38,9, 38,7, 41,6, 40,2, 39,1 and 40,6 (p >0.01); and DBP 95, 82, 75, 75, 78, 80 and 80 (p <0,01); respectively.

Conclusions: The Fimasartan kept an adequate control of the systolic and diastolic blood pressure with a decrease on the proteinuria on a medium term (56, 6% at 24 weeks), which confirms its renoprotective effect, non-antihypertensive-dependent.

***Corresponding author**

Antonio Méndez Durán. Hospitals Division, Mexican Social Security Institute. Durango No. 289, 10°. Piso. Col. Roma Norte. C. P. 06700, Delegación Cuauhtémoc, Mexico City, Mexico, USA, Tel: 57 26 17 00, extensión 17144; Email: antonio.mendezd@imss.gob.mx

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Keywords

- High blood pressure
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ABBREVIATIONS

BRA: Angiotensin II Receptor Blocker; FIMA: Fimasartan; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; DM: Type 2 Diabetes Mellitus; HBP: High Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

INTRODUCTION

The Hypertension is a worldwide public health problem, it is the most important cardiovascular risk factor associated with the greatest number of deaths in the world by all causes [1], it is the seventh leading cause of death in Mexico; the predominance of Hypertension established on the 2006 and 2012 Mexico National Survey of Health and Nutrition was of 31%, with an estimate of 22 millions of Mexicans who suffer it, of which 20% of the patients were between 20 and 35 years old and the 50% were older than 65 [2]. The activation of the renin–angiotensin–aldosterone system is responsible of producing 90% of the hypertension cases and aggravate the already established one through different mechanisms. Among the main mechanisms are the sustained vasoconstriction by the angiotensin itself and the sodium and water accumulation by the aldosterone which increase the blood volume. The drugs that block the renin–angiotensin–aldosterone system (ARBs: Angiotensin II Receptor Blockers) are the first therapeutic line on the management of the patients with High Blood Pressure [3]. Its antihypertensive efficacy, the overall

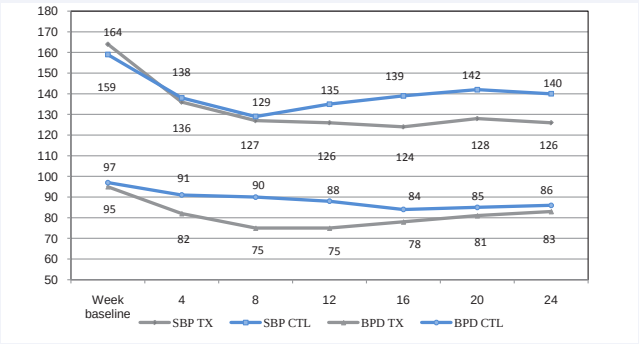

Figure 1 Evolution of systolic and diastolic blood pressure.
Note: p<0.01
Abbreviations: SBP TX: Systolic Blood Pressure Treated; SBP CTL: Systolic Blood Pressure Control; BPD TX: Blood Pressure Diastolic Treated, Blood Pressure Diastolic Control

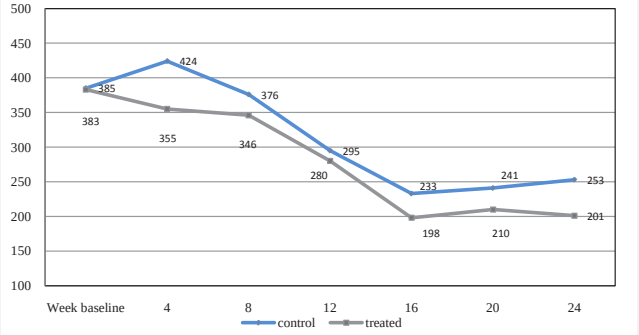

Figure 2 Behavior of albuminuria (mg/day).
Note: *p<0.01*

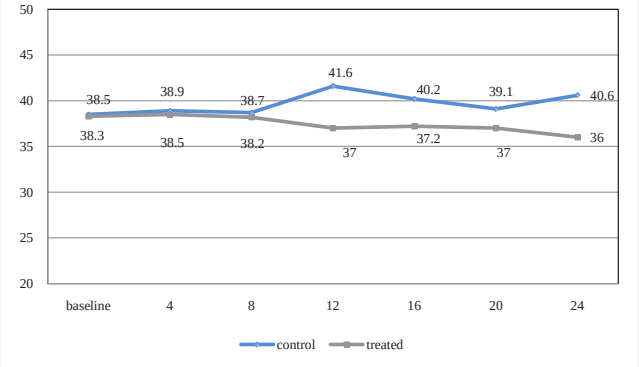

Figure 3 Evolution of Glomerular filtration rate (mL/min)
Note: *p<0.01*

security and the few side effects mostly free of giving cough place them on a pharmaceutical family with great therapeutic adherence [4,5] and consequently a very low rate of drop-out [6]. The FIMA, one of the most recent of this family, applied on the clinical practice [7], has showed efficacy and security on the management of the hypertensive patient [8]. The ARBs' pleitropic effects had defined this group of antihypertensive agents [9], nevertheless the organo protection [10,11] and specially the antiproteinuric effect has been reported as an independent effect of the hypertensive control [12]. The overall objective of the study was to identify the antiproteinuric and antihypertensive effect of Fimasartan in patients with Chronic Kidney Disease, such as type 2 Diabetes Mellitus, Hypertension, and renal failure that can end on renal damage.

MATERIALS AND METHODS

24-Week Prospective Study, conducted on outpatients from November 16, 2014 to February 16, 2015. It included adults (<18 years old) with high cardiovascular and renal risk, with High Blood Pressure or type 2 Diabetes Mellitus or both conditions; with a diagnosis of at least 10 years of one or another condition and Chronic Kidney Disease with TGF >30 mL/min according to the estimate by means of the formula MDRD (Modification of Diet in Renal Disease) or albuminuria less than 500 mg/24 h and Uncontrolled Hypertension in spite of being under treatment with another BRA.

Exclusion criteria

Patients with acute infectious events and severe uncontrolled hypertension (>150/110 mm Hg or higher). Elimination criteria: treatment discontinuation, voluntary drop-out of the study protocol, TFG worsening (>2 mL/month), increased serum creatinine (>1 mg/month), uncontrolled hypertension even with the maximum dose in FIMA monotherapy and the addition of Thiazide Diuretic. All the subjects signed an informed consent. Study variables: age, sex, comorbid diseases. Baseline seric measurements were carried out and urea, creatinine, ureic acid, albumin, calcium, phosphorus, hemoglobin, hematocrit, liver function tests and of TFG were conducted at the 4th, 8th, 12th, 16th, 20th weeks. The percentage of patients that reached the antihypertensive objective was estimated with FIMA doses of 60 and 120 mg/day at the 2nd and 4th weeks of treatment. The albuminuria determination was performed by conventional laser nephelometry, it was determined on mg/24 h. The Blood Pressure objective was to obtain a value <140/90 mm Hg and >115/75 mm Hg through a Three Step Treatment, wherein if the objective wasn´t reached on the 4th week, the FIMA dose was duplicated and in the other 4 weeks. The addition of Hydrochlorothiazide was assed also on a Three Step Treatment of 12, 5 mg/day, maximum dose of 25 mg/day.

RESULTS AND DISCUSSION

40 patients, 20 male and 20 female, with an average age of 55,9 years old (rate:30-74), 21 with primary diagnosis of type 2 Diabetes Mellitus and associated Hypertension, and 19 with Primary Systemic Arterial Hypertension and associated Chronical Renal Disease. All of the patients got an antihypertensive treatment based on Losartan 4, Enalapril 12, Metoprolol 4, Irbesartan 5, Olmesartan 5, Nifedipine 4 and Telmisartan 6, during a mean period of 15,3 months (range: 3-36) without history of optimum control of the Blood Pressure numbers.

The values at the 4th, 12th and 24th weeks, were 11,9, 12,4 and 12,6 g/dL for hemoglobin (*p: ns*); 121.5, 119 and 117.3 mg/dL for serum glucose (*p: ns*); 3,5, 3,4 and 3,7 g/dL for serum albumin (*p: ns*); 2,2, 2,1 and 2,1 mg/dL for serum creatinine; PAS:

164, 127 and 126 mm Hg (*p<0,01*) and PAD: 95, 75 and 90 mg Hg (*p<0,01*). (Figure 1); proteinuria 383, 346 and 201 mg/24 h (*p<0,01*), (Figure 2); TGF 38,5, 38,7 and 40,2 mL/min (*p<0,01*). (Figure 3); respectively.

The assessment of transaminases and Bilurubin didn't registered changes. No patient showed uncontrolled hypertension, there weren't cerebral or renal cardiovascular events during the study. It wasn't necessary neither to duplicate the FIMA dose nor to add diuretics.

The FIMA on a BRA derived from the modification of the heterocyclic ring of Losartan, is a non-peptidic antagonist of angiotensin-receptors that replaces the isoteric part of the Losartan's imidazole by the Pyrimidine-4 (3H), which gives even more potency than the Losartan itself. Approved by the Korea Food and Drug Administration in 2010 and widely used for the management of Hypertension on a slight to moderate level [13].

On a pre-clinical stage, it has been used in doses that go from 20 to 240 mg/day, with excellent results, decreasing effectively the Blood Pressure Numbers in comparison with other ARBs, such as Valsartan [14]. The antihypertensive efficacy of the FIMA on the Mexican population has been evaluated on a controlled clinical trial, involving 272 patients of 54, 9 years old, in whose was showed to reduce the Blood Pressure Numbers in a consistent way similar to the observed in other studies carried out in Korea, latter the country with the greatest clinical experience in the world [15].

This study showed the antihypertensive potency of the FIMA on a group of patients with difficult-to-control hypertension, that in spite of taking several therapeutic classes didn't reached the appropriate antihypertensive objectives. The available studies show additional benefits of the FIMA, one of them was carried out on rats exposed to Doxorubicin, chemotherapeutic elective agent on lung carcinoma, thyroid, mama, stomach, sarcoma, myeloma and lymphoma; in this experimental model was demonstrated the prevention of the progressive damage– cardiomyopathy–induced by the drug, the systemic toxicity was decreased and the survival of the rats was improved [16,17].

In patients with Metabolic Syndrome, in a FIMA real world study carried out in patients with High Blood Pressure and high cardiovascular risk, it was noted a right hypertensive control, with an improvement on some Systemic inflammatory parameters [18].

Nowadays, the aim is to compare the effects of the ARB effects vs. the calcium-antagonists. FIMA vs. Amlodipine is compared concurrently by using 18F-fluorodesoxiglucose FDG and Positron Emission Computed Tomography (PET-CT) to obtain images and establish such differences on the swelling of the atherosclerotic plaque of the carotid artery, which turns out to be encouraging for the ARB [19]. Most recently, a controlled clinical trial done with FIMA, Valsartan and Atenolol, measured the Central Blood Pressure and compared the results to create correlations and identify factors related to the Cerebral Blood Flow and the development of the Cerebral Ischemia Event on hypertensive patients [20].

FIMA, as a new molecule, has a wide range of possibilities of study in patients with high cardiovascular risk. We'll have to wait the results on a large scale that show additional benefits beyond the control of the Blood Pressure alone, raw dates that could make it a choice. In this work, the antihypertensive potency of the FIMA was confirmed in groups of patients with high cardiovascular, cerebral and renal risk.

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