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Comparison of the Antihypertensive activity of Telmisartan Versus Valsartan in Queen Alia Heart Institute/Royal Medical Services

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Abstract: Hypertension is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. The goal of antihypertensive therapy is to maintain blood pressures of < 140/90 mmHg for most people. All international guidelines for the management of hypertension recommend angiotensin receptor blockers (ARBs) as an initial or add-on antihypertensive therapy. The ARBs are very well tolerated as monotherapy as well as in combination with other anti-hypertensive medications that improve adherence to therapy and have become a mainstay in the treatment of stage 1 and 2 hypertension. The 8 available ARBs have variable clinical efficacy when used for control of hypertension. Assessment of the efficacy and safety of Telmisartan (80 mg once daily) versus valsartan (160 mg once daily) for the management of blood pressure (BP) in patients with essential hypertension. A cross sectional retrospective single center, parallel-group study. Patients will be recruited from Queen Alia Heart Institute. Data will be gathered by reviewing the medical records. Baseline characteristics were not significantly different between the two study groups. After 12 weeks, BP had fallen to a greater extent in the Telmisartan group compared to Valsartan group in terms of mean reductions in the systolic and diastolic BP of 126.2/80.4 (Adjusted change from baseline-26.8/-20.9) and 133.3/ 86.8 mm Hg (Adjusted change from baseline--18 /-12.7) ($p<0.0021$). In Stage 2 hypertensive patients once daily Telmisartan 80 mg provides significantly greater BP lowering compared to Valsartan 160 mg.
Keywords: Hypertension, Telmisartan, stroke, myocardial infarction.

INTRODUCTION

Hypertension affects around 88 million adults (≥21 years) in the United States; it is a main risk factor for stroke, myocardial infarction (MI), vascular disease, and chronic kidney disease (CKD) [1]. Hypertension may be primary, which may result as a consequence of environmental or genetic sources, or secondary, which has multiple causes, including renal, vascular, and endocrine etiologies. Essential hypertension accounts for 85-95% of adult cases, and secondary hypertension accounts for 10-15% of cases [2]. The systemic role of the rennin-angiotensin-aldosterone system (RAAS) is one of the fundamental hormonal systems in the role in the long-term control arterial pressure, volume balance and in the pathophysiology of hypertension (HTN). RAAS controls fluid and electrolyte homeostasis via harmonized effects on the cardiac muscle, blood vessels, and kidneys [3]. Therefore, when overexpressed, RAAS has long been known as a major contributor to cardiovascular disease by rising in blood volume, arterial pressure, fibrosis, a pro-thrombotic state, and progression of vascular lesions. Overexpression of the RAAS results in different injurious vascular effects [4].

The aim of antihypertensive management is to keep blood pressures of < 140/90 mmHg. If lifestyle changes are inadequate to attain the target BP, there are numerous drug choices for managing HTN. Thiazide diuretics, an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARBs), or calcium channel blockers (CCBs) are the ideal agents in non-black populations, while CCBs or thiazide diuretics are the preferred in African American hypertensive patients [5]. The angiotensin II receptor blockers (ARBs) represent an innovative category of antihypertensive drugs. Their mechanism of action differs from that of the angiotensin-converting enzyme (ACE) inhibitors, which also work on the RAAS [6]. The ARBs were introduced to overcome various deficiencies of ACEI: competitive inhibition of ACE leads to a reactive rise in renin and angiotensin I concentrations, which may overcome the blocking effect; ACE is a relatively nonspecific enzyme that has substrates as well as angiotensin I, including bradykinin and other tachykinins, and consequently, inhibition of ACE may lead to accumulation of these substrates; production of angiotensin II can arise by non-ACE pathways in addition to the primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition; definite side effects are related to ACE

inhibitor effects on the enzyme; and ARBs may give more broad angiotensin II inhibition by interacting selectively with the receptor location [7]. At present, there are eight ARBs sold for HTN. Due to their molecular variances, these agents exhibit significant difference in their pharmacokinetic and pharmacodynamic profiles, which are expected to affect clinical efficiency. These dissimilarities relate to lipophilicity, volume of distribution (VD), bioavailability, plasma $t_{1/2}$, and elimination. All 8 drugs in this class are approved by the Food and Drug Administration (FDA) for the management of HTN, either alone or in combination with other drugs (Table 1) [8]. Besides providing greater tolerability over ACEI, clinical studies have also confirmed that the ARBs, in particular Telmisartan, deliver greater BP lowering to ACEI in the early morning in addition to the 24-hour, morning, day-time and night-time periods [9]. Telmisartan is a once-daily ARB having the longest plasma $t_{1/2}$ of any ARB, (24 h coverage) of BP management from a single daily dosage; the angiotensin type 1 (AT1) compared with AT2 receptor affinity ratio for Telmisartan is 3000-fold; however, it is higher for Valsartan (around 20,000-fold). As the most lipophilic of the ARBs, Telmisartan moreover has the highest VD, which enables tissues penetration [10]. The purpose of this study was to compare the antihypertensive effects between Telmisartan and Valsartan in uncomplicated hypertensive subjects.

Table-1: Pharmacologic Characteristics of the Angiotensin Receptor Blockers

ARBs	Half-life (h)	Tmax (h)	Bioavailability	Route of elimination: renal (R) biliary/fecal (B)	Food Interaction	Drug Interactions	CYP metabolism
Losartan	2.1	1.1–1.5	34%	36% R; 59% B	Yes	Rifampin, fluconazole	2C9, 3A4
Candesartan cilexetil	9.3	1.5–4.5	41%	34% R; 68% B	No	None	2C9 (negligible)
Eprosartan	5.1–9.1	1.1–3.2	64%	8% R; 89% B	Yes	None	No
Irbesartan	11.2–15.1	1.5–3.3	59–81%	21% R; 81% B	No	None	2C9, 3A4 (negligible)
Telmisartan	24	0.6–1.1	44%	<1% R; >98% B	No	Digoxin	No
Valsartan	5.8	2.1–4.1	24% (capsule) 52% (solution)	14% R; 43% B	Yes	None	2C9 (weak)
Olmesartan medoxomil	12.2–14.3	1.8–2.6	27%	36–52%R; 49–64% B	No	None	No
Azilsartan medoxomil	12.4	1.4–2.9	61%	41% urine; 56% B	No	None	2C9, CYP2B6 CYP2C8 (negligible)

MATERIALS AND METHODS

We used a computerized database in this retrospective observational study. Data were retrieved from the patients' medical records in Queen Alia Heart Institute at the Royal Medical Services (RMS) in Amman/Jordan. Ethical approval has been obtained from the IRB committees at the RMS. Inclusion criteria were newly diagnosed or known hypertensive patients who were not taking antihypertensive drugs for more than the last month. Patients were excluded if they had one or more of the following; Serum Potassium >5.5 mg/dl, serum creatinine >1.5 mg/ dL, HbA1c above 8.0%, secondary HTN, on hormonal or steroid therapy, on oral hypoglycemic agent or lipid-lowering drug, coronary artery disease or atherosclerotic disease and suffering from nervous, gastrointestinal disease, or malignant disease. Results of blood chemistry and complete blood count were accessed through revision of patient's medical profiles. The aim of this study was to determine whether Telmisartan 80 mg administered once daily was inferior or superior to Valsartan 160 mg for the control of BP measured in the clinic following 12 weeks of treatment. Patients in which systolic pressure was >140 mm Hg or diastolic pressure was >90 mm Hg were defined as having HTN. The primary endpoints for assessing efficacy were the changes from baseline to 12 weeks period SBP and DBP.

STATISTICAL ANALYSIS

The data were analyzed using the Statistical Package for the Social Sciences, version 22 (SPSS). The comparison of qualitative data was done by using ANOVA (repeated measure). The data were expressed as mean± SD. A p-value <0.05 was considered statistically significant.

RESULTS

223 patients had stage 2 HTN at baseline (140/90 mm Hg) were included in this study (Telmisartan n= 112, Valsartan n= 111). Baseline characteristics of the patients are shown in Table 2 and 3. There were no differences in baseline characteristics observed among the two study groups. Mean age of the total population of patients with stage 2 HTN was 57 years and mean seated baseline BP was 153.45/100.2 mm Hg. Mean body mass index was 31.55 kg/m^2, and the majority (73.8%) of patients were aged <65 years. Most of the patients were males (56%).

Table-1: Comparison of baseline parameter in the both study groups

Parameter	Telmisartan 80 mg	Valsartan 160mg
Age, years (SD)	58.1 (10.9)	55.9 (9.6)
Age group, N (%) < 65 years (SD) > 65 years (SD)	 82 (73.2) 30 (26.7)	 81 (72.9) 30 (27.1)
Gender, N (%) Male Female	 65 (58) 47 (42)	 60 (54) 51 (56)
Weight (SD)	70.8 (10.3)	72.1 (10.8)
BMI (SD)	31.2 (4.9)	31.9 (7.6)
SBP, mm Hg (SD)	153.2 (18.9)	151.7 (16.1)
DBP (mm Hg) (SD)	101.1 (11.4)	99.3 (10.5)
HbA1C (SD)	5.8 (0.7)	5.6 (0.4)
Pulse rate, beats/min (SD)	75.7 (9.9)	75.0 (9.4)

BMI- Body Mass Index, HbA1c- Glycated hemoglobin, SBP: systolic blood pressure, DBP: diastolic blood pressure • Values indicates Mean±SD

Table-3: Blood chemistry and complete blood count baseline in the both study groups

Test	Telmisartan 80 mg (n=112)	Valsartan 160mg (n=111)
BUN (mg/dl)	13.2±4.2	12.7±3.5
SCr (mg/dL)	0.91±0.012	0.89±.011
Na (mEq/L)	136±18.9	135.1±21.2
K (mEq/L)	4.4±1.13	4.1±1.08
Ca (mg/dl)	8.01±0.26	10.32±0.39
PO4 (mg/dl)	3.9±0.8	3.52±0.71
Hemoglobin (g/dL)	12.8±3.7	11.95±3.98
Hematocrit %	38.1±7.02	37.3±5.12
MCV (fL)	89±7.6	89.3±6.19
RBCs (10^6/uL)	4.8±0.73	4.45±0.68
Platelets (10^3/uL)	215±45.9	221±65.4
WBCs (10^3/uL)	6.01±1.7	6.6±1.53

MCV, Mean Corpuscular Volume; RBC, Red Blood Cell Count; WBC ; White Blood Cell Count. Values indicates Mean±SD

Comparison of anti-Hypertensive Efficacy

The effects of the treatment on mean BP among the studied patients with stage 2 hypertension are after 12 weeks of treatment shown in Table 4. BP was significantly decreased in both study groups (P value < 0.05). Reduction in mean BP with Telmisartan 80 mg was −21.2/−14.1 mm Hg. Treatment with Valsartan 160 mg induced reductions in mean BP was –18.4/−12.1 mm Hg. Treatment with Telmisartan 80 mg was associated with a significantly greater mean reduction in BP compared with Valsartan 160 mg for both SBP (adjusted mean difference −2.6 mm Hg; (P value 0.0241) and DBP (adjusted mean difference −2.0 mm Hg; P value 0.0232).

DISCUSSION

Results of the present study, has shown that management of HTN with Telmisartan 80 mg dropped SBP and DBP to a significantly greater degree than management with Valsartan 160 mg. As anticipated, both study groups lowered BP to a significantly greater level in comparison to baseline. These results are consistent with previous studies that revealed decreases in BP with Telmisartan therapy [11]. After 12 weeks of HTN therapy, a final mean SBP/DBP <140/90 mm Hg has been achieved in about half of the patients with stage 2 HTN, indicating a clinically imperative achievement in this high-risk patient group. Moreover, this study revealed that different ARBs treatment had an influence on BP outcomes and goals.

Table-4: Mean BP and changes from baseline by study groups.

	Telmisartan 80 mg (n = 112)	Valsartan 160 mg (n = 112)
SBP, mm Hg		
Baseline (SD)	153.2 (18.9)	151.7 (16.1)
P value between the 2 study groups	0.486	
End of study (SD)	126.2 (15.1)	133.3 (15.5)
P value in the same study group	<0.001	<0.001
Change from baseline (SD)	-27 (11.3)	-18.4 (12.3)
Adjusted change from baseline (SE)	-26.8 (0.9)	-18 (0.9)
Comparison to Telmisartan 80 mg	-8.8 (P value 0.034)	
DBP, mm Hg		
Baseline (SD)	101.1 (11.4)	99.3 (10.5)
P value between the 2 study groups	0.365	
End of study (SD)	80.4±8.3	86.8±9.8
P value in the same study group	<0.001	<0.001
Change from baseline (SD)	-20.7 (8.8)	-12.5 (9.9)
Adjusted change from baseline (SE)	-20.9 (0.56)	-12.7 (0.51)
Comparison to Telmisartan 80 mg	8.2 (P value 0.0021)	

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation; SE: standard error

Treatment with Telmisartan was significantly more effective than Valsartan in terms of the proportion of patients who achieved a BP goal of <140/90 mm Hg. In earlier studies comparing Telmisartan versus Valsartan as monotherapy in equivalent doses, Telmisartan was more potent to achieve more persistent BP control, with both greater 24 h BP decrease. This may be clarified by the pharmacokinetic profile of Telmisartan, which has a longer $t_{1/2}$ (24 h) compared with valsartan (6 h) [12]. The level of the changes in BP reductions seen in our study in stage 2 HTN patients between the two study groups is clinically important. Mean reductions in BP were more than 20/10 mm Hg. Furthermore, the differences between Telmisartan and Valsartan were of clinical significance. Telmisartan has a superior BP trough-to-peak ratio in the range of 0.6-1.1 as well as having the largest Vd (500 L), the toughest binding affinity, and the longest duration of receptor blocking effect in comparison with other agents of ARBs [13]. Moreover, Telmisartan has a rapid onset of action (maximum plasma levels are attained 0.6-1.1 hours after administration) [14]. Additionally, using ambulatory BP checking, Telmisartan 80 mg is superior to Valsartan 160 mg in the last 6 hours of the dosing interval. A previous pooled review of 2 studies in patients with mild to moderate HTN showed that Telmisartan 80 mg provided SBP reductions in the last 6 hours of the dosing interval and in the 24-hour mean that were superior to the equipotent valsartan 160 mg (by 2.7 and 2.0 mm Hg, respectively) [15]. Furthermore, two new studies have revealed that Telmisartan 80 mg was superior to valsartan 160 mg [16, 17]. However, there are few studies comparing Telmisartan and Valsartan as a monotherapy. In a meta-analysis of more than one million adults from 60 studies [18], the association between BP reduction and cardiovascular morbidity and mortality suggests that a decrease in SBP of just 2 mm Hg would afford a 10% decrease in stroke mortality and 7% lower mortality from ischemic heart disease (IHD). In a previous study that evaluated observational statistics from two large population cohorts, a 2 mm Hg reduction in DBP was shown to be related with an 11% reduction in risk of IHD and a 16% reduction in stroke [19].

CONCLUSION

In conclusion, in patients with a newly diagnosed essential HTN, once-daily the use of long-acting ARBs such as Telmisartan was significantly more effective than equipotent Valsartan during the last 6 hours of the 24-hour dosing interval, and provide improved BP control.

REFERENCES

1. Sierra C, de la Sierra A. Antihypertensive, cardiovascular, and pleiotropic effects of angiotensin-receptor blockers. Current opinion in nephrology and hypertension. 2005 Sep 1;14(5):435-41.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. Jama. 2003 May 21;289(19):2560-71.
3. Cice G, Di Benedetto A, D'Isa S, D'Andrea A, Marcelli D, Gatti E, Calabrò R. Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure: a double-blind, placebo-controlled trial. Journal of the American College of Cardiology. 2010 Nov 16;56(21):1701-8.
4. Burnier M. Telmisartan: a different angiotensin II receptor blocker protecting a different population?.

Journal of International Medical Research. 2009 Dec;37(6):1662-79.
5. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),” Journal of the American Medical Association. 288(23); pp. 2981–2997, 2002.
6. Lacourcière Y, Krzesinski JM, White WB, Davidai G, Schumacher H. Sustained antihypertensive activity of telmisartan compared with valsartan. Blood Press Monit. 2004;9:203–210.
7. Hirata K, Vlachopoulos C, Adji A, O'Rourke MF. Benefits from angiotensin-converting enzyme inhibitor 'beyond blood pressure lowering': beyond blood pressure or beyond the brachial artery? J Hypertens. 2005;23:551–556.
8. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. Journal of the American Society of Echocardiography. 2005 Dec 1;18(12):1440-63.
9. White WB, Calhoun DA, Samuel R, Taylor AA, Zappe DH, Purkayastha D. Improving blood pressure control: increase the dose of diuretic or switch to a fixed-dose angiotensin receptor blocker/diuretic? The valsartan hydrochlorothiazide diuretic for initial control and titration to achieve optimal therapeutic effect (Val-DICTATE) trial. thE JOUrNaL Of CLiNiCaL hypErtENsiON. 2008 Jun;10(6):450-8.
10. Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ. 2011;342:d2234.
11. White WB, Punzi HA, Murwin D, Koval SE, Davidai G, Neutel JM. Effects of the angiotensin II receptor blockers telmisartan vs valsartan in combination with hydrochlorothiazide 25 mg once daily for the treatment of hypertension. The Journal of Clinical Hypertension. 2006 Sep;8(9):626-33.
12. White WB, Lacourciere Y, Davidai G. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure: impact on the early morning period. American journal of hypertension. 2004 Apr 1;17(4):347-53.
13. Costa FV. Telmisartan. High Blood Pressure & Cardiovascular Prevention. 2006 Sep 1;13(3):85-94.
14. Jung AD, Kim W, Park SH, Park JS, Cho SC, Hong SB, Hwang SH, Kim W. The effect of telmisartan on endothelial function and arterial stiffness in patients with essential hypertension. Korean circulation journal. 2009 May 1;39(5):180-4.
15. Lacourciere Y, Krzesinski JM, White WB, Davidai G, Schumacher H. Sustained antihypertensive activity of telmisartan compared with valsartan. Blood pressure monitoring. 2004 Aug 1;9(4):203-10.
16. Mallat SG. What is a preferred angiotensin II receptor blocker-based combination therapy for blood pressure control in hypertensive patients with diabetic and non-diabetic renal impairment?. Cardiovascular diabetology. 2012 Dec;11(1):32.
17. Al Sabbah Z, Mansoor A, Kaul U. Angiotensin receptor blockers-advantages of the new sartans. Journal of the Association of Physicians of India. 2013 Jul;61:464-70.
18. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 60 prospective studies. Lancet 2002, 360:1903-1913.
19. Kakuta H, Sudoh K, Sasamata M, Yamagishi S. Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor: comparison with other angiotensin II type 1 receptor blockers. International journal of clinical pharmacology research. 2005;25(1):41-6.