Medico Research Chronicles

ISSN No. 2394-3971

Original Research Article

ANTI-INFLAMMATORY EFFECTS OF TELMISARTAN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND HYPERTENSION

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Submitted on: February 2015
Accepted on: February 2015
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Abstract

Objective: To determine the effect of angiotensin receptor blocker (Telmisartan) on C reactive protein reduction in patients with type 2 diabetes mellitus and hypertension.

Study Design: Cross-sectional descriptive study.

Place and Duration of Study: Department of Medicine of Khyber Teaching Hospital Peshawar.

Methodology: After approval from the hospital ethical and research committee the study was conducted and it included 112 patients recruited through non probability consecutive sampling. A written and informed consent was taken and patients were subjected to detailed history and clinical examination after which the base line CRP was measured. Then they were started on Telmisartan at a dose of 40mg per day. Patients were followed up at 6th week of starting treatment and the level of CRP was measured again. Data was analyzed using SPSS Version 16.

Results: Out of the 112 patients included in the study 57% were females and 43% were males. Mean age was 49.46 9(SD±10). The average CRP level before commencement of the treatment was 5.98 mg/dl (SD±1.8) while levels after 6 weeks of treatment the level fell to an average of 4.5mg/dl (SD±2). In 67% of the patients the drug was found to be efficacious while in 33% the drug was not effective.

Conclusion: Telmisartan is efficacious in reducing the C-reactive protein levels in patients with type2 diabetes mellitus and hypertension.

Key words: Telmisartan, C-reactive protein, Diabetes Mellitus, hypertension

Introduction

Diabetes mellitus is an emerging health issue worldwide being the fifth leading cause of death and causing about 3 million deaths every year[1]. Diabetes and hypertension together are important risk factor for coronary atherosclerosis, inflammation is said to be the major underlying pathogenic mechanism and C-reactive protein (CRP) is the most extensively studied marker of inflammation in this regard[2].

Angiotensin receptor blockers are inhibitors of the renin angiotensin system by blocking the effect of Angiotensin-2 on its target receptors[3, 4]. Angiotensin 2 in turn is said to be a powerful mediator of vascular inflammation and can promote atheroma formation in the vessels, as such these drugs being the inhibitors of the renin angiotensin axis are said to possess additional anti-inflammatory properties in addition to its anti-hypertensive effect[5, 6]. Evidence is available to the facts that both Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) do not only have similar effects on blood pressure control but also more importantly are potential CRP lowering drugs and improve prognosis in atherosclerotic patients[7,8].

The effect ARBs in Asian population has not been studied, further more they are not widely prescribed drugs in colored races due to their poor antihypertensive effects in this set of patients[9]. The aim of the study was to update local knowledge about the efficacy of ARBs and its potential as an anti-inflammatory agent. The results of this study will help us in designing recommendation for their routine use in diabetic and hypertensive patients at risk for coronary artery disease.

Methodology

Our study was undertaken in The Department of Medicine of Khyber Teaching hospital Peshawar. The duration of study was 6 months from July 2014 till December 2014.

After approval from the hospital ethical and research committee the study was conducted and it included patients recruited through non probability consecutive sampling, presenting to the OPD, aged more than 40 years with diabetes and hypertension of more than 5 years duration and having baseline CRP of ≥2mg/dl. A written and informed consent was taken and patients were subjected to detailed history and clinical examination after which the base line CRP was measured. Then they were started on Telmisartan at a dose of 40mg per day provided from hospital bait-ul-maal facility. Patients were followed up at 6th week of starting treatment and the level of CRP was measured again. The efficacy of the drug was measured in terms of at least 1mg/dl reduction or more of the CRP from the baseline. The data was analyzed using SPSS Version 16. Mean was calculated for quantitative variables like age and CRP levels while descriptive statistics were applied to the categorical variables like gender and efficacy and stratification done amongst various age groups. Post-stratification was done using Chi-square test and keeping p-value less than 0.05 as significant.

Results

Among the total 112 patients examined 57% were females and 43% were males. Mean age was 49.46 (SD ±10). Minimum age was 40 and maximum age was 80.

Among different age groups 41.1% belonged to age group 40to 50 years, 47.3% belonged to age group 51 to 60 years,8.9% aged 61 to 70 years and 2.9% belonged to 71 to 80 years age group. Mean CRP level before the treatment was 5.98% (SD±1.8). Mean post CRP level was 4.5 %(SD±2).

In 67% of the patients included in the study the drug was found to be efficacious while in 33% the drug was ineffective in reducing the levels of CRP (Table 1).

The data was stratified in to various age groups to assess the impact of drug on CRP reduction different age groups. According to our study in the first group aged 40-50yrs., out of the total 46 patients in 33 (71.8%) the drug was found to be efficacious while in 13 (28.2%) the drug was not found to be effective. In the second strata aged 51-60yrs. 37 (69.9%) showed the drug to be effective.

In the third group 61-70yrs among a total of 10 patients 6(60%) showed no effect on the CRP reduction while 4(40%) showed a positive response.(table2) In the last group 70-80 yrs. out of a total of 3, 2pateints (66.7%) had no effect the CRP levels while 1 patient (33.3%) showed a positive response (Table 2).

The data was also stratified among males and females. Among the total 48 male patients 34(70.8%) the drug was efficacious while in the 14(29.2%) the drug was ineffective. Similarly among the total no. of females 41(64.1%) out of 64 showed a positive response while the remaining 23(35.9%) had no effect on the CRP level.

Discussion

Diabetes mellitus and hypertension are two important risk factor for atherosclerosis, due to the significant mortality and morbidity associated with it this particular matter has been a subject of intense research. Recent advances have shown that vascular inflammation is in part mediated by the Angiotensin II and increased plasma levels of angiotensin II and the resultant increase in the activity of angiotensin II receptors promote the progression and severity of atherosclerosis. This when combined with hyperlipidemia can increase the risk of plaque progression even in the absence of hemodynamic influences [10, 11, 12].

Angiotensin receptor blockers serve to block the action of Angiotensin II at the receptor level negating its effects and it is this action which is an added advantage for the use of these agents in relatively younger diabetic patients at risk for atherosclerosis[13].

The anti- inflammatory effect of ARBs has been elucidated in a number of trials with some conflicting results. The mean reduction of C-reactive protein is different for each member of the Angiotensin receptor blocker group. The most first and most important of these trials was the Val-MARC (Valsartan- Managing Blood Pressure Aggressively and Evaluating Reductions in hs-CRP) trial [14]. This study included two subsets of Patients, one group received Valsartan alone while the other received combination of Valsartan and Hydrochlorthiazide. After 6 weeks of therapy the Valsartan group showed a significant reduction in the CRP levels. This finding is consistent with the results of our study performed on Telmisartan, another drug of the same category showing a decrease in the levels of CRP levels after 6 weeks of therapy.

Similarly in other trials implicating Telmisartan same effect was observed. In a recent study performed by Koulouris[15] et al the effect of Telmisartan and Ramipril on lipid peroxidation and inflammation was assessed and it was found that both agents caused a significant reduction of the CRP as well as that of the lipid peroxidation ($p<0.001$).

Although not evaluated in our study due to lack of appropriate laboratory facilities, Telmisartan is unique among the other members of its class on account of its added metabolic advantages. It is a potent stimulator of peroxisome proliferator-activated receptor-γ (PPAR-γ), which is an intracellular regulator of lipid and glucose metabolism mediating anti-inflammatory effects on the vascular smooth muscle cells[16, 17, 18]. Telmisartan may thus be beneficial in improving glucose metabolism, Triglyceride levels and insulin sensitivity. This effect further strengthens the need for routine use of Telmisartan in patients with type2 diabetes mellitus in whom the major underlying pathologic mechanism is metabolic syndrome. This effect has been studied in the ongoing ONTARGET [19] *(ongoing telmisartan alone and in combination with ramipril global endpoint trial)* confirming the positive impact of Telmisartan on the metabolic parameters of the study population.

Despite a growing body of evidence implicating a promising role of Telmisartan in cardiovascular risk reduction, in many other large multicenter trials using C-reactive protein as a marker of inflammation, Telmisartan was shown to show little or no effect on its levels e.g. in the VIVALDI[20,21] *(investigate the efficacy of telmisartan versus valsartan in hypertensive type 2 Diabetics)*, it was found that both valsartan and Telmisartan were unable to effect the CRP levels to any appreciable extent. However as regards the blood pressure control Telmisartan was found superior to valsartan [22]. The results of this and some other trials contrast sharply to those of our study in which a small but appreciable decrease in the level of C-reactive protein was observed after 6 weeks of full dose therapy. This discrepancy could in part be due to the genetic variability of the study population. Almost all of the studies performed on the effect of ARBs on the C-reactive protein levels were performed on the Caucasians. The levels of angiotensin II are genetically determined thus altering the response of drugs in colored races. To date no such study has been performed in our population and future trials are warranted to explore the full potential of Angiotensin receptor blockers in our setup.

Conclusion

Telmisartan can retard the process of atherosclerosis by reducing the C reactive protein levels and thus the underlying inflammatory process as such they should be prescribed in relatively younger patients with diabetes and hypertension who are at an increased risk for atherosclerosis.

Table 1: Gender-wise efficacy of Telmisartan of CRP Reduction by atleast1mg/dl.

Gender of patients	Drug efficacy (yes)	Drug efficacy (no)	Total
Male	34 (70.8%)	14 (29.2%)	48
Female	41 (64.1%)	23 (35.9)	64
Total	*75 (67%)*	*37 (33%)*	*112*

Table 2: Age group-wise efficacy of Telmisartan in reducing CRP level by at least 1mg/dl.

Age of the patients	Drug efficacy (yes)	Drug efficacy (No)	Total
40-50 yrs	33 (71.8%)	13 (28.2%)	46
51-60 yrs	37 (69.9%)	16 (30.1%)	53
61-70 yrs	4 (40%)	6 (60%)	10
71-80 yrs	1 (33.3%)	2 (66.7%)	3
Total	*75*	*37*	*112*

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