UNIVERSITY OF THESSALY SCHOOL OF MEDICINE LABORATORY OF BIOMATHEMATICS M.SC. "RESEARCH METHODOLOGY IN BIOMEDICINE, BIOSTATISTICS AND CLINICAL BIOINFORMATICS

MASTER THESIS

«A protocol for an observational study for telmisartan in the treatment of patients with hypertension »

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TABLE OF CONTENTS

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ABSTRACT

Background: Telmisartan has effective treatment of hypertension in a broad spectrum of hypertensive patients offering the advantage of very long half-life and enables blood pressure control over 24 hours using once-daily administration.

Aims: To evaluate the efficacy of telmisartan in daily clinical practice and to assess whether or not telmisartan elicits beneficial effects on the progression of microalbuminuria in normotensive and hypertensive patients.
Setting and Design: Observational 4-week clinical study

Materials and Methods: Hypertensive and normotensive outpatients with type 2 diabetes and microalbuminuria were started on telmisartan 40 mg/day with optional up-titration to 80 mg/day in order to achieve seated systolic (SSBP) and diastolic (SDBP) blood pressure <140/90 mm Hg.
Intent-to-treat and per protocol efficacy assessment was based on SSBP/SDBP reduction and delivered doses.

Results: SSBP/SDBP was decreased and patients showed lower transition rates from microalbuminuria to overt nephropathy compared to the placebo group. In normotensive patients treated with telmisartan, changes in urinary albumin-to-creatinine were not significantly correlated with changes in blood pressure. The present study demonstrates that telmisartan prevents the progression of microalbuminuria in normotensive patients with type 2 diabetes.

Conclusion: Telmisartan is shown to be safe and well tolerated in these patients.

INTRODUCTION

Hypertension (HT) is a well-established risk factor responsible for cardiovascular disease (CVD) and chronic kidney disease (CKD). High blood pressure (BP) is associated with development of CVD in a continuous manner; risk increases with incremental BP, even within the normal range. Hypertension is one of the main causes of death worldwide and has emerged as increasingly important medical and public health issue. It affects approximately 25% of the adult population worldwide, and its prevalence is predicted to approach the 60% by 2025 (Keamay et al., 2005) It is considered as a treatable risk factor for:

- coronary heart disease (CHD) ,
- congestive heart failure (CHF),
- ischemic
- haemorrhagic stroke ,
- renal failure
- peripheral arterial disease (PAD)

According to the Seventh Report of the Joint National Committee (JNC-7) on prevention, detection, evaluation and treatment of high blood pressure, systolic blood pressure (SBP) > 140 mmHg is a crucial risk factor for CVD than diastolic blood pressure (DBP) in subjects of > 50 years old. Clinical trials and observational studies suggest that poor systolic blood pressure control is largely responsible for the unacceptably low rates of overall blood pressure control. Systolic blood pressure control rates appeared less of 60–70% while diastolic blood pressure control rates exceeded 90% in the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (Jones et al., 2000; Cushman et al.,2002; Midha et al., 2010; Black et al., 2001; Weir, 1998).

Patients with hypertension often present glucose tolerance with hypertension and diabetes mellitus and at the same time the symptomatology include also renal failure, early development of cardiovascular disease, and premature death. (Go et al., 2004). Kidney is a vital target organ in both hypertension and diabetes, with late studies uncovering that microalbuminuria is an early clinical marker of nephropathy, as well as a crucial indicator of cardiovascular occasions in both nondiabetic and diabetic population .Particular efforts are made to diminish urinary albumin excretion as the danger of cardiovascular morbidity and mortality increases with expanding urinary excretion of albumin with no conspicuous threshold or plateau (Manolis et al.,2004).

Numerous patients with fundamental hypertension may give clear or sub-clinical target organ damage (TOD) including heart, kidneys, central nervous system or retina at the season of their underlying analysis (Cuspidi et al., 2004). The assessment of sub-clinical TOD has turned into the key component in assessing hypertensive patients. Microalbuminuria (MA) is connected with high rate of morbidity expressing a condition of expanded renal endothelial dysfunction and is viewed as an early marker of diffuse endothelial permeability. Since reducing albuminuria delays the progression of the dysfunctions , this parameter can be utilized for measuring the adequacy of the various therapies.

In the course of the most recent couple of decades, the Renin Angiotensin system (RAS) has been a medication focused on cardiovascular and renovascular diseases. The two classes of medications that target the RAS are the Angiotensin converting enzyme (ACE) inhibitors and the specific AT1 receptor blockers (ARBs). Both ACE inhibitors and ARBs are powerful antihypertensive drugs that have been appeared to reduce the danger of cardiovascular and renal dysfunctions (O'Hare et al., 2000).

Angiotensin II receptor blockers (ARBs) are powerful antihypertensive drugs and are broadly viewed as having tolerability profiles like that of placebo. (Lacourciere et al.,2003) Of the available ARBs, Telmisartan has the longest half-life of around 24 h (Lefebvre et al., 2002) This proposes Telmisartan ought to have a long throughout the once-daily dosing interval. Another component recognizing Telmisartan from different ARBs is its high lipophilicity. (Littlejohn et al., 2002) This improves tissue penetration, intracellular absorption and bioavailability. The high lipophilicity of Telmisartan, in correlation with losartan, may give vascular protection (Mallion et al., 1999)

Another component that recognizes Telmisartan from the ARBs candesartan, Cilexetil, losartan, is that it is not a prodrug; consequently antihypertensive intensity is related to the activity of the parent compound (Nishimura et al., 2005). Most studies are of short duration, with one and only long term investigation of 1-year span. The suggested beginning dose of Telmisartan for the vast majority with hypertension is 40 mg once every day. Taking into account the pulse reaction and/or Telmisartan symptoms, the dosage might be expanded or diminished. With every adjustment in dosage, it might take a few weeks to see the full impact of Telmisartan on bringing down pulse. The suggested dose of Telmisartan for reducing the danger of cardiovascular issues, in individuals at high risk for such issues is 80 mg every day (Markham et al., 1997).

The issue of masked hypertension can be exacerbated in people getting treatment for hypertension, in light of the fact that numerous antihypertensive medications have an impact at trough that is significantly lower than their peak effect. In fact, in the 1990s when most currently utilized antihypertensives were assessed, the US Food and Drug Administration's measure for a powerful antihypertensive drug was one with a through–peak ratio of no less than 50% (Meredith and Elliott, 1994).

Therapeutic methodologies to moderate declining kidney work and to avert cardiovascular events ought to go for both large reductions in blood

pressure (BP) and diminished rinary albumin excretion (Neutel etal., 2003). Angiotensin receptor blockers (ARBs) have protective effects on kidney in patients with diabetic nephropathy, but monotherapy with a standard dose of ARB is frequently inadequate to accomplish the suggested BP goals (Nalbantgil et al., 2004; White et al., 2004; Sharm et al., 2007)

A reasonable examination among different antihypertensive specialists can't be built up exclusively on the premise of trough– pinnacle proportions (Lefebvre et al 2002). Since the drug is typically directed once every day and taken in the morning to support persistent consistence, peak efficacy is likely to happen around the time of morning blood pressure estimation in the doctor's office. By complexity, the trough impact may agree with the early morning time frame towards the end of the dosing interim. Therefore, patients with treated hypertension regularly have generally higher morning blood pressure contrasted and office bloodpressure. (Redon et al 2002).

Clinical guidelines have suggested threshold levels for the usage of antihypertensive treatment, normally taking into account blood pressure levels (Chobanian et al 2003; Guidelines Committee 2003; Whitworth 2003). Angiotensin II receptor blockers (ARBs) are profoundly powerful antihypertensive drugs and are generally viewed as having great tolerability (Meredith 2005).Of the commercially available ARBs, telmisartan has the longest half-life of about 24 h (Burnier and Maillard 2001; Brunner 2002). Telmisartan, is a long-acting angiotensin receptor blocker (ARB), having therapeutic effects that go beyond blood pressure control, as a non-peptide AT1 receptor antagonist, orally active, highly selective, potent (Burnier, Maillard 2001; Brunner 2002; Wienen et al 2000).

Among the class of AT1 receptor antagonist, telmisartan offers the advantage of very long half-life. Telmisartan ought to have a long activity, in this way guaranteeing blood pressure control all through the once-day by day dosing interval. Another component recognizing telmisartan from different

Angiotensin II receptor blockers is the fact that presents high lipophilicity conferring vascular protection (Wienen et al 2000; Takai et al 2005). This fact increase, also, its penetration on various tissues, its intracellular absorption and bioavailability, reflecting in the high volume of distribution of approximately 500L (Stangier et al 2000). Another feature is that it is not a prodrug and as a consequence antihypertensive potency is related to the activity of the parent compound (Wienen et al 2000;Stangier et al 2000).

The hypertensive and normotensive people display a comparative circadian variation in blood pressure, levels being high at the daytime and low in the middle of the night (Staessen et al 1997; Elliot et al., 1998). On arousing, the blood pressure surges, however the degree of this surge can change in various people with some showing morning hypertension (Gosse et al 2004). In different subjects, blood pressure is increased at the evening time and hypertension holds on in the morning. An immediate connection exists between SBP on arising and left ventricular mass (Gosse et al 1997), and the SBP on emerging has been appeared to be rather higher in the subjects who have cardiovascular complications (Gosse et al 2001, 2004). Multivariate examination found that the relationship between early morning blood pressure and cardiovascular risk was autonomous of age and 24 h circulatory strain. A relationship has been shown between a high early morning blood pressure surge and microalbuminuria (Polonia et al 2005).

Also various studies have observed that treatment with ARBs or ACEIs results in long-term stabilization or standardization of albuminuria in normotensive type 2 diabetic patients . In any case, no complete largescale study has researched regardless of whether angiotensin blockade prevents the progression of albuminuria in normotensive patients with type 2 diabetes. This examination ought to be especially essential since it has been revealed that Japanese diabetic patients are substantially more powerless than Caucasians to end-stage renal disease (Hirose, 2005). It was recenlty observed that the Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study to

analyze the impact of telmisartan, an ARB, on the progression of microalbuminuria in Japanese patients with type 2 diabetes . This study included 163 normotensive and 351 hypertensive patients. The significant finding was that telmisartan treatment adequately reduced the transition rate from incipient to obvious nephropathy in Japanese type 2 diabetic patients (Viberti et al., 2002; Wachtell et al., 2003).

Data collected in various European and Non European Countries, together with the BP values reported in large-scale intervention trials, demonstrate that at the best close to 25–30% of treated hypertensive patients display during treatment BP values beneath 140/90 mmHg and that these figures are worse in diabetic or nephropathic hypertensive patients, in which BP objectives are, as indicated by the suggestions of late European Guidelines, < 130/80 mmHg. Also other studies have shown that the extent of patients with controlled BP has been appeared to be low in patients with a cardiovascular risk profile (past myocardial localized necrosis, diabetes, metabolic disorder, renal deficiency), which by definition would require more noteworthy cardioprotection. Recenlty, some change in BP control has been accounted for, especially in England. Also BP control is similarly poor when evaluated through the sphygmomanometric system or via semi-automatic or ambulatory BP monitoring (ABPM) method (Mallion et al., 1999; Clemente et al., 2003)

The main features of an ideal antihypertensive agent. Are

- Greater blood pressure lowering effects
- Better blood pressure control
- Balanced action throughout 24 hours
- Greater cardiovascular protection (brain, heart and kidney)
- Efficacy in a broad range of subjects
- Tolerability profile at least comparable to existing agents
- Properties to enhance patient’s compliance
- Sympathomodulatory and cardioprotective properties

- Neutral or favorable metabolic effects
- Evidence for long-term benefits
- Potential utility across cardiovascular continuum of responders increases with increasing daily drug dosage up to 40–80 mg/day and ranges from 69–81%.

(Williams et al., 2009)

The % of treated patients achieving a target sitting DBP < 90 mmHg (i.e. the normalisation rate) also increases with the dosage, at the 80 mg daily dose amounting to about 64–84%.1,10

One randomised, double-blind multicentre study evaluated long-term telmisartan administration in patients with isolated systolic hypertension, showing in more than 50% of the treated hypertensives a target reduction in SBP, defined as a systolic value < 140 mmHg or a decrease of > 20 mmHg. (Neutel, 2003;2005). These figures have been confirmed by a number of studies performed by employing 24-hour ABPM, which additionally documented both in uncomplicated and complicated hypertension (renal insufficiency, renal failure, diabetes mellitus, obesity as well as metabolic syndrome) that

1) the drug effectively reduces BP values throughout the 24-hour average interval,

2) the antihypertensive effect follows the circadian rhythm of BP, allowing protection of the cardiovascular system against the early morning BP rise and its adverse effects on the heart and vital organs(Cohen, 1997).

A growing body of evidence indicates that renoprotective effects of ARBs and ACEIs not only in hypertensive exist also in normotensive diabetic patients. The ACE-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects (ATLANTIS) study demonstrated that treatment with ramipril had no effect on glomerular filtration rate, but significantly

decreased microalbuminuria in normotensive type 1 diabetic patients. Similarly, captopril significantly decreased albuminuria in normotensive type 1 diabetic patients with albuminuria >300 mg/d. Further study showed that an ARB—losartan, irbesartan, or valsartan —significantly decreased urinary albumin excretion in normotensive type 2 diabetes.(Teo et al., 2004)

A comparison of telmisartan versus losartan in hypertensive type 2 Diabetic patients with overt nephropathy (AMADEO) – was designed to determine whether pharmacological differences between telmisartan and losartan would translate into larger and more durable reductions in proteinuria over time. Compared with losartan (an ARB already approved for diabetic nephropathy to prevent renal disease progression), (Zandbergen et al., 2003), the highly lipophilic ARB telmisartan has a longer halflife and displays approximately 25% greater angiotensin II type 1 receptor binding (Burnier,2001).

The multicenter, double-blind, prospective study was performed in 860 hypertensive (SBP/DBP >130/ 80 mmHg or receiving antihypertensive medication at baseline) patients with type 2 diabetes and who had a morning spot urinary protein-to-creatinine ratio 700 mg/g or more. After a placebo run-in period, the randomized patients received either telmisartan 40 mg or losartan 50 mg for 2 weeks, followed by telmisartan 80 mg or losartan 100 mg, respectively, for 50 weeks. The magnitude of the reduction in proteinuria expressed as UACR at 52 weeks – the primary endpoint – was significantly greater with telmisartan (29.8%) compared with losartan (21.4%; P ¼ 0.027) (Bakris et al., 200e, 2008).

Recent evidence describe that it is not just hard to accomplish sphygmomanometric (or center) BP control additionally to extend this control to different parameters, (for example, home BP) which assume a noteworthy part in deciding the long term risk of fatal and nonfatal cardiovascular events. Finally, data gathered with regards to the European Lacidipine Study on Atherosclerosis have demonstrated that it is difficult to accomplish as well as to keep up a BP control in the long term period. The antihypertensive efficacy

of telmisartan (20–160 mg/day) and its capacity to accomplish satisfied BP control have been all around recorded in randomized, multicentre studies about, the treatment length with a duration of 4–52 weeks. The antihypertensive impact of the medication is generously present within 1–2 weeks of starting treatment, accomplishing a plateau after 8–10 weeks and being from that point well maintained

At the present study we plan to evaluate the efficacy of telmisartan in daily clinical practice and to assess whether or not telmisartan elicits beneficial effects on the progression of microalbuminuria in normotensive and hypertensive patients. The study will have a duration of 4-week observation of the patients.

The sample will be hypertensive and normotensive outpatients with type 2 diabetes and microalbuminuria starting telmisartan 40 mg/day with optional up-titration to 80 mg/day in order to achieve seated systolic (SSBP) and diastolic (SDBP) blood pressure <140/90 mm Hg. Intent-to-treat and per protocol efficacy assessment was based on SSBP/SDBP reduction and delivered doses

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