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Medicine

TELMISARTAN: A CARDIO-METABOLIC SARTAN

Nayan Dutta	Golaghat Nursing Home, J G Path,golaghat Town, Assam, 785621
Neeraj Tulara*	Dr. L H Hiranandani Hospital, Hill Side Avenue, Hiranandani Garden, Powai, Mumbai -400076 *Corresponding Author
Nilesh Banthia	Vishparbha Society, Near Shivaji Chowk, Behind Axis Bank, Vasudev Balwant Phadke Rd, MCCH Society, Panvel, Navi Mumbai, Maharashtra 410206
P. Chakradhar	Meenakshi Hospital, D No:7-1-151,near Old Bus Tand, Jagityal, Karimnagar505327
Pradeep Sreedhar	Sridhars Diacare B.G. Road, Chakkorathkulam, Westhill. P.O, Calicut - 673005

KEYWORDS :

Hypertension occurs approximately twice as frequently in patients with diabetes compared with patients without diabetes. Conversely, hypertensive persons are more likely to develop diabetes than normotensive persons. Besides, up to 75% of cardiovascular disease in patients with diabetes may be attributed to hypertension, leading to recommendations for more aggressive blood pressure control in persons with coexistent diabetes and hypertension[1]. Given the current pandemic of obesity and diabetes mellitus type 2 in both developed and developing countries, the usage of antihypertensive drugs with beneficial metabolic properties in the treatment of arterial hypertension becomes of great clinical challenge. ß -blockers and diuretics have been found to have a detrimental influence on insulin sensitivity and glucose metabolism, calcium channel blockers seem to be metabolically neutral, while angiotensin-converting enzyme inhibitors and angiotensin receptors blockers (ARBs) may improve metabolic profile[2].

Telmisartan is an ARB that is highly selective for the AT1 receptor and has a long duration of action because of its long terminal elimination half-life[3]. Telmisartan is more useful for controlling morning hypertension than valsartan when given once daily in the morning. Therefore, telmisartan is thought to be more advantageous than other ARBs in protecting the internal organs of patients with morning hypertension[4]. In addition to antagonizing AT1 receptors, telmisartan has the unique property of activating PPAR- γ, thereby improving insulin sensitivity and reducing triglyceride levels. Telmisartan also induces adiponectin protein expression in adipocytes at a post-transcriptional level, leading to an increase in adiponectin plasma levels. These effects have been found to improve metabolic syndrome and reduce the risk of atherosclerosis[3,5]. Telmisartan has structural similarities to antidiabetic agent pioglitazone (a peroxisome proliferator-activated receptor- γ (PPAR γ) agonist). Activation of PPAR γ regulates carbohydrate and lipid metabolism and influences the inflammatory processes[2]. PPAR- γ influences the gene expression involved in carbohydrate and lipid metabolism[6]. The absolute oral bioavailability of telmisartan has been found to be 42% and 47% for the tablet and oral solution of telmisartan 40 mg, respectively; and > 57% for telmisartan 160 mg. Telmisartan in serum has been found to be > 99.6% protein-bound, with the degree of protein binding remaining constant over a wide concentration range. Binding is mainly due to human serum albumin, but binding to other serum proteins (α -1-acid glycoprotein) has also been detected[3]. The terminal elimination half-life value was 13.6 h after oral administration in normotensive subjects. Pharmacokinetic evaluation of telmisartan in mild-to-moderate hypertensive patients showed a terminal half-life of ~24 h. The long terminal half-life of telmisartan supports a once-daily dosing regimen and suggests that drug concentrations do not decline below therapeutic levels even if a dose is delayed. Excretion of telmisartan is predominantly by the fecal route, with > 90% of the oral dose excreted within 120 h. Telmisartan is cleared by the formation of a glucuronic acid conjugate and subsequent elimination is via bile[7].

Various studies have led to the conclusion that ARB is a potential alternative treatment to ACE inhibitors for vascular protection, with better patient tolerability. ONTARGET[7] and TRANSCEND[8] clinical studies are the largest clinical trial program ever conducted with an angiotensin receptor blocker, telmisartan.

ONTARGET compared the ARB telmisartan alone, or in combination with the ACE inhibitor ramipril, with ramipril treatment, for the protection against major cardiovascular events such as cardiovascular death, myocardial infarction (MI), stroke, or hospitalization for heart failure. The role of ARBs in such patients is unknown. The study focused on comparing the ACE inhibitor ramipril, the ARB-telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes. 8576 patients were assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mm Hg greater reduction) and the combination-therapy group (a 2.4/1.4 mm Hg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94 to 1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, P<0.001) and angioedema (0.1% vs. 0.3%, P = 0.01) and a higher rate of hypotensive symptoms (2.6% vs. 1.7%, P<0.001); the rate of syncope was the same in the two groups (0.2%). In the combination-therapy group, the primary outcome occurred in 1386 patients (16.3%; relative risk, 0.99; 95% CI, 0.92 to 1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%, P<0.001), syncope (0.3% vs. 0.2%, P = 0.03), and renal dysfunction (13.5% vs. 10.2%, P<0.001). It was concluded that telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. However, the combination of the two drugs was associated with more adverse events without any increase in benefit[9].

The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) assessed whether the angiotensin-receptor blocker telmisartan would be effective in patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage[7]. 5926 patients, were randomized to receive telmisartan 80 mg/day (n=2954) or placebo (n=2972) by the use of a central automated randomization system. The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure. The median duration of follow-up was 56 months and it was found that mean blood pressure was lower in the telmisartan group than in the placebo group throughout the study (weighted mean difference between groups 4·0/2·2 [SD 19·6/12·0] mm Hg). 465 (15·7%) patients experienced the primary outcome in the telmisartan group compared with 504 (17·0%) in the placebo group (hazard ratio 0·92, 95% CI 0·81–1·05, p=0·216). One of the secondary outcomes—a composite of cardiovascular death, myocardial infarction, or stroke—occurred in

384 (13·0%) patients on telmisartan compared with 440 (14·8%) on placebo (0·87, 0·76–1·00, p=0·048 unadjusted; p=0·068 after adjustment for multiplicity of comparisons and overlap with primary outcome). 894 (30·3%) patients receiving telmisartan were hospitalized for a cardiovascular reason, compared with 980 (33·0%) on placebo (relative risk 0·92, 95% CI 0·85–0·99; p=0·025). Thus, it was concluded that telmisartan was well tolerated in patients unable to tolerate ACE inhibitors.

In addition to these trials, the renal-protective effect of telmisartan was established in a Japanese clinical trial. The INNOVATION (Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy) trial was designed to evaluate the efficacy of telmisartan in preventing the transition from microalbuminuria to overt nephropathy[7]. A total of 527 patients with Type 2 diabetes and microalbuminuria were randomly assigned to receive a placebo or telmisartan 40 or 80 mg/day. The results of the INNOVATION trial showed that during 1.3 ± 0.5 years of follow up, the transition rate to overt nephropathy was 16.7% with telmisartan 80 mg/day (n = 168), 22.6% with telmisartan 40 mg/day (n = 172) and 49.9% with placebo (n = 174; both telmisartan doses versus placebo, p < 0.0001).

The results of these large trials suggest that ARBs may reduce the incidence of new-onset type 2 diabetes in high-risk patients compared with other classes of antihypertensive agents. Although, in these trials, the development of diabetes was not a primary endpoint and also most of these trials were not placebo-controlled. Nevertheless, there was a clear overall trend for a lower rate of diabetes in patients treated with ARBs[3]. It is suggested to be due to the fact that angiotensin II may adversely affect glucose metabolism via mechanisms. Some studies suggested that angiotensin II might negatively modulate insulin-mediated actions by regulating multiple levels of the insulin signaling cascade such as the insulin receptor, insulin receptor substrate (IRS) and PI3K[10].

Saga Telmisartan Aggressive Research (STAR) is a single-arm, prospective multi-center trial conducted to evaluate the effectiveness of treatment with telmisartan in patients with hypertension with a focus on the effect of telmisartan on lipid and glucose metabolism[11]. A total of 197 patients with hypertension enrolled in this study and were prescribed telmisartan 20 – 80 mg/day for 6 months. Overall, in addition to blood pressure reduction, telmisartan treatment achieved a 6% reduction in total cholesterol levels and a 9% reduction in LDL-cholesterol levels. High-density lipoprotein (HDL) cholesterol levels did not change. Surprisingly, an 18% reduction in total cholesterol levels was shown in a subset of patients with baseline levels of ≥ 220 mg/dl. Also, the cholesterol reduction by telmisartan was found to be similar to the effect that can be achieved by statins. In addition, total cholesterol levels were reduced (12%) even in patients receiving statins. Moreover, when telmisartan was exchanged for other ARBs in patients with total cholesterol levels ≥ 220 mg/day, there was still a striking cholesterol reduction (24%). Triglyceride levels decreased (35%) in patients with levels of ≥ 150 mg/dl. These results suggest that telmisartan may have favorable effects on lipid metabolism in addition to lowering blood pressure. The profound effect of telmisartan to lower cholesterol suggests a potential use in hypertensive patients with dyslipidemia. Although, the mechanism of total cholesterol and LDL-cholesterol lowering in response to telmisartan is not well understood and is supposed to be a unique property of telmisartan in comparison to other ARBs. The suggested mechanism involves the inhibition of net cholesterol absorption via its PPAR- γ –activating effect[3].

Effects of telmisartan on glucose and lipid metabolism as well as blood pressure lowering via its dual-functional property – PPAR- γ activation and AT1 blocking – imply a potential benefit for the treatment of the metabolic syndrome. The basis of metabolic syndrome is visceral obesity and adipocytokines produced by visceral adipose tissues. Visceral adipose cells are large cells that produce more pro-atherogenic adipocytokines, such as leptin, resistin, TNF- α and FFA, and less of antiatherogenic adipocytokine adiponectin compared with small-sized subcutaneous adipose cells. Thus, decreased adiponectin due to large-sized adipose cells plays a key role in the pathogenesis of metabolic syndrome[3]. Clinical data showed that telmisartan treatment increased adiponectin levels, and also improved glucose and lipid metabolism and blood pressure lowering[11]. Metabolic syndrome is strongly associated with insulin resistance and consists of a constellation of factors that raise the risk of cardiovascular diseases and diabetes mellitus.

CONCLUSION

Telmisartan activates PPAR- γ as well as antagonizing AT1 receptors; thus, it has a greater beneficial effect on glucose and lipid metabolism than other ARBs. Telmisartan ameliorates insulin resistance and dyslipidemia, thus it could provide even more effective options for preventing end-organ damage and cardiovascular disease in patients with hypertension. Telmisartan has potential benefits for the treatment of hypertension when it is accompanied by abnormal glucose metabolism and/or dyslipidemia. Owing to its unique metabolic and cardiac effect, telmisartan is truly a cardio-metabolic sartan.

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