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MULTIFACETED TELMISARTAN: CANDIDATE FOR NEW THERAPEUTIC APPROACHES

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INTRODUCTION

Telmisartan is an Angiotensin II type 1 (AT1) receptor blockers (ARBs), that is highly selective for the AT1 receptor and has a long duration of action because of its long terminal elimination half-life[1]. Telmisartan is considered to be the most potent member of the sartan group because, in addition to AT1R blockade, it strongly activates the anti-inflammatory nuclear receptor, peroxisome proliferator-activated receptor γ (PPAR γ)[2]. PPAR-γ receptors are involved in the down-regulation of expression of several inflammatory cytokines and inhibition of inflammation[3]. These agents have benefits that go beyond blood pressure control and there is emerging evidence that ARBs have cardiovascular-, ocular-, cerebral- and renal-protective effects via inhibition of the renin-angiotensin activation at the tissue level, an autocrine/paracrine effect[1].

Telmisartan is a highly lipid-soluble, non-tetrazole derivative, with a single carboxylic acid group instead of a large tetrazole ring. Telmisartan bears an interesting structural resemblance to an insulin sensitizer, pioglitazone, a thiazolidinedione ligand of PPAR- γ. Negatively charged groups, such as the carboxylic base in telmisartan or the thiazolidinedione ring in pioglitazone, may contribute to PPAR- γ activation. The absolute oral bioavailability of telmisartan was 42% and 47% for the tablet and oral solution of telmisartan 40 mg, respectively; and > 57% for telmisartan 160 mg. Telmisartan in serum was > 99.6% protein-bound, with the degree of protein binding remaining constant over a wide concentration range. The binding was mainly to human serum albumin, but binding to other

serum proteins (α -1-acid glycoprotein) has also been detected. 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. Completed and ongoing clinical trials [ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial); TRANSCEND (Telmisartan Randomized Assessment Study in ACE-I Intolerant Patients with Cardiovascular Disease); PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes); INNOVATION (Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy)] that span the cardiovascular continuum are attempting to define these long-term benefits. These trials suggest that telmisartan has beneficial effects on glucose metabolism and suggest that this effect depends on effective activation of PPAR- γ and not just AT1 receptor blockade. In most of the telmisartan clinical trials that showed improved glucose metabolism. Telmisartan effectively reduced not only triglyceride levels but also total cholesterol and LDL cholesterol levels. The profound effect of telmisartan to lower cholesterol suggests a potential use in hypertensive patients with dyslipidemia. Further, type 2 diabetes and insulin resistance accompanies the absolute or relative lack of insulin, which results in triglyceride hydrolysis in adipose tissues via increased hormone-sensitive lipase activity and increased free fatty acid (FFA) release from adipose tissues. A large amount of FFA enters the portal vein to be taken up by the liver. From the FFA, triglyceride synthesis is promoted by acyl-coenzyme A (acyl-CoA) in the liver and very-low-density lipoprotein (VLDL) is released into the bloodstream. In addition, in the insulin-resistant state, lipoprotein lipase (LPL) activity is decreased and catabolism of triglyceride-rich remnants (such as VLDL or chylomicrons) is impaired. These processes lead to increased triglyceride levels and decreased HDL-cholesterol levels. This condition is known as Hypertrigriceridaemia. PPAR- γ activation of telmisartan may also contribute to its hypotriglyceridaemic action. PPARs – PPAR- α as well as PPAR- γ – play a role in intracellular lipid metabolism by upregulating the expression of the enzyme involved in the conversion of fatty acid in acyl-CoA esters, fatty acid entry into mitochondria, and peroxisomal and mitochondrial fatty acid catabolism. PPAR- γ induces LPL expression in adipose tissue, which also leads to a reduction in triglyceride levels. As telmisartan has a high affinity for hepatic tissue, its clinical dose may exhibit PPAR- α action in the liver, which may be another possible mechanism of lowering total cholesterol and LDL-cholesterol levels. 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. This syndrome is characterized by the clustering of insulin resistance, dyslipidemia, and hypertension, and is associated with increased risk of cardiovascular disease and Type 2 diabetes. 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 the metabolic syndrome. Clinical data showed that telmisartan treatment increased adiponectin levels, and also improved glucose and lipid metabolism and blood pressure lowering[1].

In recent years, evidence has accumulated for a major role in oxidative stress and neuro-inflammation in the pathogenesis and progression of Parkinson's disease (PD). The peptide angiotensin II (AII), via type 1 receptors (AT1), is one of the most important known inducers of inflammation and oxidative stress produces reactive oxygen species (ROS) by activation of the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complex and plays a major role in the pathogenesis of several age-related degenerative diseases. There is a local renin-angiotensin system (RAS) in the brain, and NADPH oxidase, AT1 and AT2 receptors have been located in dopaminergic (DA) neurons, nigral microglia and astrocytes[3]. Recognized as one of the oldest phylogenetic hormone systems, the RAS is vital for the control of systemic blood pressure, salt appetite, and aldosterone formation. In addition to the systemic effects of a RAS, many organs express components of the RAS, indicative of local tissue angiotensin-formation system[4].

Telmisartan ameliorates inflammation in various brain disorders through AT1 blockade and PPARγ activation. Soluble β-amyloid oligomers (AβOs) play a causative role in neuronal dysfunction and memory loss in Alzheimer's disease. Telmisartan ameliorates inflammatory responses in AβO-stimulated microglia. Telmisartan not only inhibited AβO-induced proinflammatory interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) expression, but also increased anti-inflammatory IL-10 expression, which was not affected by AβO stimulation. Telmisartan also inhibited AβO induced nuclear factor (NF)-κB activity and phosphorylation of Akt and ERK, two upstream regulators of NF-κB activation[2]. AT1 is localized in the multiple structures of the brain. Many studies revealed a physiological role of AT1 receptors in the regulation of the cerebral vasculature and therefore blood flow to the brain, the central and peripheral sympathetic system, hormone production and release, and behavior. The AT1 receptor is a participant in multiple brain functions[5]. It is proposed that the neuroprotective effects of telmisartan are associated with its direct AT1R blockade effects[6].

The ARB group is heterogeneous, with some members, notably Telmisartan and to a lesser extent Candesartan, exhibiting a pleiotropic profile, not only blocking AT1 receptors but also activating PPAR γ, an anti-inflammatory, pro-metabolic nuclear receptor. The key role of increased AT1 receptor activation as an early, and perhaps fundamental injury factor in brain disorders is amply substantiated by the discovery that the AT1 receptor blockade protects mitochondrial function in cerebrovascular endothelial cells exposed to oxidative stress and other early injury mechanisms [5]. Wang et al. found that telmisartan is a very promising neuroprotective compound and substantiates the therapeutic use of this drug in neurodegenerative diseases and traumatic brain disorders where glutamate neurotoxicity plays a significant role. Telmisartan ameliorates glutamate-induced cell injury is associated with inhibition of glutamate-induced ERK1/2 phosphorylation and with the reversal of glutamate-induced suppression of phosphorylated Akt and GSK-3b

Similarly, various parts of the eye express the components of the RAS, suggesting that the eye contains an AngII formation system that is separate from that functioning systemically. Dysregulation of the RAS has been implicated in retinal vascular diseases such as retinopathy of prematurity and diabetic retinopathy. The importance of the RAS in retinal function has been implied from a large number of studies demonstrating positive effects when inhibitors of ACE or antagonists

to AT1R are used in the treatment of retinal diseases, such as diabetic retinopathy or retinopathy of prematurity. Ang II is known to regulate neural function in the brain. It is likely, that neurons within the retina, being part of the CNS, are similarly modulated. Diabetic retinopathy is the leading cause of blindness in those of working age and is characterized by the development of progressive vascular pathology within the inner retina. Recent studies suggest that nearly all patients with Type I and over 60% of those with type II (non-insulin dependent) diabetes will develop non-proliferative diabetic retinopathy, and 20-30% of these patients will progress to vision-threatening forms of the disease. The earliest signs of diabetic retinopathy include the breakdown of the blood-retinal barrier, loss of pericytes and the formation of microaneurysms, which are small outpouchings of the blood vessel wall. With the progression of diabetic retinopathy, an increasing number of hemorrhages become apparent that may be associated with other signs of retinal ischemia including the presence of cotton wool spots. Proliferative diabetic retinopathy is associated with the growth of new blood vessels on the surface of the retina. Vision loss can occur from vitreous hemorrhaging or tractional retinal detachment that developments in late stages of the disease. Macular edema is another significant cause of vision loss in those with diabetes. It develops following the breakdown of the blood-retinal barrier and leakage of fluid into the macula. It is well recognized that patients with hypertension are at greater risk of developing diabetic retinopathy. In addition, blockade of the RAS is known to reduce the incidence and progression of diabetic nephropathy and cardiovascular complications of diabetes. The use of ARB in diabetic animal models has been found to reduce the risk of diabetic retinopathy. However, this needs to be further investigated in detail[7].

CONCLUSION

A metabolic sartan, telmisartan has potential benefits for the treatment of hypertension when it is accompanied by abnormal glucose metabolism and/or dyslipidemia. Blockade of AT1 and PPR γ receptors by telmisartan offers a variety of novel and safe therapeutic approach for the treatment of illnesses of increasing prevalence and socioeconomic impact, such as diabetic neuropathy, neurodegenerative diseases of the brain along with the treatment in cardiac and diabetic condition. Telmisartan is a metabolic sartan that may be utilized as a powerful tool for cardio-diabetic complications.

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