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Telmisartan and Stroke Reduction in the ONTARGET Trial: Benefit beyond Blood Pressure Lowering?

Victor L. Serebruany^a, Dan Atar^b, Dan F. Hanley^a

^aHeartDrug™ Research Laboratories, Johns Hopkins University, Towson, Md., USA; ^bAker University Hospital and Faculty of Medicine, University of Oslo, Oslo, Norway

The recently published *ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial* (ONTARGET) was a phase IV randomized study which enrolled 25,620 high-risk patients with coronary heart disease or diabetes plus additional risk factors, who were over the age of 55 years of age but did not have evidence of heart failure [1]. Patients were randomized to receive either the ACE-inhibitor ramipril (10 mg/day), the angiotensin receptor blocker (ARB) telmisartan (80 mg/day), or their combination. The mean duration of follow-up of the study was 55 months. The primary composite outcome was the time to the first event of cardiovascular death, myocardial infarction (MI), stroke, or hospitalization for heart failure. It occurred in 16.5% of patients treated with ramipril, in 16.7% of those treated with telmisartan, and in 16.3% of patients randomized to combination therapy (table 1). The ONTARGET investigators conclude that telmisartan was equivalent to ramipril in high-risk patients with vascular disease or diabetes. The combination of the two drugs was associated with more adverse events without an increase in clinical outcomes benefit.

Even though the evidence presented in table 1 reveals a level of nonsignificance for the difference of the various outcome measures among the three treatment arms, the incidence of strokes may deserve further scrutiny. In absolute numbers, there were 405 strokes (4.7%) in the ramipril arm, compared with 369 strokes (4.3%) in the telmisartan arm. In the combination group, there were 373 strokes (4.4%). In fact, this finding represents an 8.5% stroke reduction with ARB when compared with the ACE inhibitor. Considering the straight-forward and robust study design of ONTARGET and its long follow-up over 4 years, we suspect that this mild trend towards a decrease in strokes does not represent a random play of chance. Furthermore, when those antihypertensive agents were used in combination, the trend towards fewer strokes remains consistent, representing a 6.4% risk reduction as compared to monotherapy with the ACE inhibitor, despite the more potent antihypertensive effect. Since there is a lack of association between the degree of blood pressure lowering and the incidence of strokes, the ONTARGET data may point to other distinct underlying mechanism(s) responsible for the mild stroke

reduction with ARB, beyond blood pressure control. In the following deliberations, we would like to put forward what we think is an attractive hypothesis for such a mechanism.

The trend towards stroke reduction may be attributed to the ability of ARBs to mildly inhibit platelet activity. In fact, platelets contain angiotensin II receptors within their surface membranes [2] and, therefore, ARBs may affect platelet activity directly targeting these specific receptors. Indeed, in vitro data strongly suggest antiplatelet properties of not only the prodrugs from the ARB class, but their principal metabolites as well [3]. Moreover, these results have been confirmed in a small randomized study suggesting ex vivo platelet inhibition by ARBs in patients with mild to moderate hypertension [4]. Treatment with valsartan (80–360 mg/day) over 9 weeks resulted in a consistent inhibition of adenosine diphosphate-induced conventional platelet aggregation, and prolonged closure time by the PFA-100 Platelet Analyzer. In addition, therapy with ARB has been associated with a downregulation of the expression of numerous platelet surface receptors such as glycoprotein Ib, glycoprotein IIb/IIIa activity, vitronectin receptor, p-selectin, LAMP-1, and CD40-ligand.

It will be critical to know whether the minuscule, yet potentially appealing stroke reduction signal observed in ONTARGET will translate into significant stroke prevention in such a megatrial as PROfESS [5]. These data are expected soon, and will be critical for the comprehension of better ways to prevent recidivating strokes. The focus is on maintaining the optimal balance between the utilization of blood pressure-lowering medications and platelet inhibitors to protect such high-risk patients from repeated vascular events.

Table 1. ONTARGET key outcomes

Outcome	Ramipril (n = 8,576) %	Telmisartan (n = 8,542) %	Combination (n = 8,502) %
CV death/MI/stroke/ CHF hospitalization	16.5*	16.7	16.3
CV death/MI/stroke	14.1	13.9	14.1
MI	4.8	5.2	5.2
Stroke	4.7	4.3	4.4
CHF hospitalization	4.1	4.6	3.9
CV death	7.0	7.0	7.3
Any death	11.8	11.6	12.5
Renal impairment	10.2	10.6	13.5

* All nonsignificant among groups. CV = Cardiovascular; CHF = congestive heart failure.

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Dr. Viktor L. Serebruany
HeartDrug™
Research Laboratories
Johns Hopkins University
Osler Medical Building, 7600 Osler Drive, Suite 307
Towson, MD 21204 (USA)
Tel. +1 410 847 9490, Fax +1 443 583 0205, E-Mail heartdrug@aol.com

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Atypical Cases of Posterior Reversible Encephalopathy Syndrome

Clinical and MRI Features

Satyakam Bhagavati^a, Jai Choi^b

^aDepartment of Neurology and ^bNeuroradiology Division,
Department of Radiology, SUNY Downstate Medical Center,
Brooklyn, N.Y., USA

Posterior reversible encephalopathy syndrome (PRES) describes a neurological syndrome with multiple described causes and is characterized by headache, altered mental status, seizures or loss of vision [1]. The typical imaging findings are hyperintensities on magnetic resonance (MR) FLAIR images in the parieto-occipital, posterior frontal cortical and subcortical white matter. The brain stem, basal ganglia and cerebellum are less commonly involved. The pathogenetic mechanism of this entity is poorly understood. One hypothesis states that surges of hyperperfusion in hypertensive patients, primarily in the vertebrobasilar circulation, due to impaired autoregulation lead to extravasation of fluid and vasogenic edema [2]. Alternatively, it has been proposed

that vasoconstriction and hypo-perfusion cause ischemia and edema [3, 4].

We describe here 2 atypical cases of PRES which may shed some light on possible cerebrovascular pathogenetic mechanisms. One patient with a history of pre-eclampsia presented with uncommon MR imaging (MRI) findings of a pontine lesion and multifocal constrictions of the basilar, posterior cerebral and carotid arteries and their branches, suggestive of vasospasm. The other one, in an acute alcoholic stupor, had a potentially new cause of PRES. We emphasize the vasoconstrictive response which may underlie the pathogenesis of PRES in patients with diverse etiologies.

Case 1

A 21-year-old woman presented 10 days postpartum after induction of vaginal delivery for severe pre-eclampsia at 39 weeks of gestational age. She complained of severe, generalized headaches for 1 day and transient episodes of blurred vision and a feeling of numbness of the right side of her face which lasted about 5 min. On examination the blood pressure was 160/120 mm Hg. The only neurological abnormality noted was bilateral hyperreflexia in both the upper and lower extremities. A cranial T₂-weighted MRI scan revealed an abnormal, hyperintense signal in the pons (fig. 1a). No other cerebral lesions were noted. MR angiography showed focal constriction of the mid basilar artery (fig. 1b) and the cavernous portion of the right internal carotid artery (fig. 1c). Multifocal stenoses (beads-on-string appearance) of branches of the anterior and posterior cerebral arteries were also noted (fig. 1b, c). The blood pressure was controlled with antihypertensive medication. Extensive workup for vasculitis (including antinuclear antibodies, anti-DNA antibodies, rheumatoid factor) was negative. The patient showed rapid improvement in her symptoms over 3–4 days. A repeat MRI and MR angiography scan after 4 weeks was normal with complete resolution of the pontine lesion and all vascular abnormalities.

Case 2

A 57-year-old patient with a history of chronic alcohol abuse, who had been found by his wife to be walking unsteadily and in a confused state, suddenly collapsed and did not respond to commands. A history of consumption of large amounts of whisky for the past 2 days was provided by the wife. He was rushed to the emergency room. On examination the blood pressure was 131/88 mm Hg and the daily blood pressure readings over the following 2 weeks remained normal. He was minimally responsive to painful stimuli and did not react to verbal commands. The blood alcohol level was very high (358 mg/dl). Toxic screen did not reveal any other drugs. Cranial MRI FLAIR images done at the time of admission revealed bilateral cortical and subcortical, parieto-occipital and posterior frontal hyperintense lesions (fig. 1d). MR angiography did not show any abnormalities. A repeat cranial MRI scan after 2 weeks was normal with resolution of all lesions (fig. 1e) and complete clinical improvement.

Discussion

PRES can occur due to many causes including acute severe hypertension, pre-eclampsia and eclampsia, renal disease, immunosuppressive and cytotoxic drugs (such as cyclosporine and tacrolimus), collagen vascular disorders like systemic lupus erythematosus and hematological disorders such as thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome [1]. Re-