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Treatment with telmisartan/rosuvastatin combination has a beneficial synergistic effect on ameliorating Th17/Treg functional imbalance in hypertensive patients with carotid atherosclerosis

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ABSTRACT

Objectives: To explore synergistic effect between angiotensin II receptor blockers (ARBs) and statins on Th17/Treg functional imbalance in hypertensive patients with carotid atherosclerosis.
Methods: This study was a 2×2 factorial randomized, prospective, double-blind, placebo-controlled trial. One hundred and fifty nine hypertensive patients with carotid atherosclerosis were randomized to the administration of control group, telmisartan group, rosuvastatin group, and combination group (telmisartan plus rosuvastatin) base on hydrochlorothiazide treatment. Carotid ultrasonography, parameters of Th17/Treg functional axis, interleukin (IL)-1β, IL-2, interferon (IFN)-γ, hypersensitive C-reactive protein (hsCRP), monocyte chemotactic protein (MCP)-1 were evaluated.
Results: Blood pressure level markedly reduced in four groups. There was significantly synergistic effect of combination of telmisartan with rosuvastatin on reducing carotid imtima-media thickness (IMT), Th17 cells frequency, IL-17, IL-6, IL-23, tumor necrosis factor (TNF)-α, expression of retinoic acid receptor-related orphan receptor (ROR)γt mRNA, Th17/Treg ratio, IL-1β, IL-2, IFN-γ, hsCRP, and MCP-1, and increasing Treg cells frequency, IL-10, transforming growth factor(TGF)-β1, and expression of forkhead/winged helix transcription factor (Foxp3) mRNA (all $P < 0.05$). Change rate of IMT statistical positively related to descent rates of Th17 cells frequency, IL-17, IL-6, IL-23, TNF-α, expression of RORγt mRNA, Th17/Treg ratio, IL-1β, IL-2, IFN-γ, hsCRP, and MCP-1, and negatively related to increased rates of Treg frequency, IL-10, TGF-β1, and expression of Foxp3 mRNA, respectively (all $P < 0.05$).
Conclusion: There is a synergistic effect of combination of telmisartan with rosuvastatin on ameliorating Th17/Treg functional imbalance in hypertensive patients with carotid atherosclerosis.
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1. Introduction

Atherosclerosis, the principal origin leading to significant mortality and morbidity, is a subtle, chronic and low-grade inflammatory disease [1,2]. Hypertension and dyslipidemia exert crucial pathogenic roles on atherosclerotic processes, including activation of immune cells and inflammatory cytokines [3,4].

Current dogma holds that Th1/Th2 balance is central to the chronic inflammation in initiation and development hypertension and atherosclerosis [3,5]. However, in recent years, the classical paradigm of Th1/Th2 balance has been challenged by the recognition of Th17/Treg balance [6–12]. Distinct from Th1 and Th2 subsets, Th17 and Treg cells have been identified as two novel independent CD4+ T cell subsets [10]. As with Th1/Th2 profiles, counterbalancing mechanisms in the local environment may contribute to Treg/Th17 mediated responses [8]. Studies demonstrated that there was a remarkable Th17/Treg functional imbalance in patients with acute coronary syndrome and unstable carotid atherosclerotic plaques [6,11,12]. And this functional imbalance was confirmed in ApoE−/− mice model [7].

Angiotensin (Ang) II, one of vital components of renin-angiotensin system (RAS), is a major contributor to the development and maintenance of hypertension and atherosclerosis [10]. It could be produced by lymphocytes and triggers the proliferation of

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splenic lymphocytes through angiotensin II type 1 (AT1) receptor activation [13,14]. Madhur and coworkers [15] demonstrated that Th17 number and IL-17 production obviously increased in mice after angiotensin II infusion.

Angiotensin II receptor blocker (ARB) has been demonstrated to have additional anti-inflammatory properties, such as lowering plasma levels of inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, and tumor necrosis factor-α (TNF-α), beyond blood pressure (BP) lowering [16–19]. However, Rajagopalan and colleagues [20] reported that valsartan (one of the ARBs) alone did not reduce plasma level of hsCRP in hypertensive patients with hyperlipidemia.

Statin, competitively inhibit HMG-CoA reductase, exhibits wide variety of nonlipid or pleiotropic effects. It is a novel mean of attenuating inflammatory processes independently of its action on reducing blood lipids [21–23]. It was reported that treatment targeting the RAS in combination with statin augments the antihypertensive effects of the ARB while simultaneously preventing the progression of atherosclerosis and suppressing autoimmune processes [20,24].

It is well known that carotid artery ultrasound provides an "observation window" for systemic atherosclerosis in humans. High-resolution B-mode ultrasound measurement of the carotid imtima-media thickness (IMT) not only provides important information for early diagnosis and prognosis of atherosclerotic disease, but also has considerable significance for assessing and predicting cardiovascular health and disease risk [25]. Particularly, ultrasound measurements of carotid artery IMT are reproducible means to assess atherosclerotic vessel wall changes [26].

However, to the best of our knowledge, the effects of this combination treatment on Th17/Treg functional balance have not been explored in further. Our goal was to explore whether or not there is additive or synergistic effect of combination of ARBs with statins on improving Th17/Treg functional imbalance in hypertensive patients with carotid atherosclerosis.

2. Materials and methods

2.1. Study design and patients

This study was a 2×2 factorial randomized, prospective, double-blind, placebo-controlled trial of BP and lipid lowering on the incidence of cardiovascular events among hypertensive patients with carotid atherosclerosis. The inclusion criteria were: (1) ages ranged from 35 to 79 years, (2) a sitting systolic (S)BP/diastolic (D)BP was 140/90 mmHg or over, (3) carotid IMT was 1.0 mm or over. Patients were excluded for any of the following reasons at the time of screening: secondary hypertension, diabetes mellitus, history of cardiac or cerebral attack (including transient ischemic attack), congestive heart failure, renal failure and dialysis treatment, chronic viral infection, acute respiratory infection, intestinal infection, dental problems, connective tissue diseases, any anti-inflammatory treatment, malignancy, any type of surgery in the past week, definite hypersensitivity or contraindication to the study medications, pregnancy, drug and alcohol abuse, inability to walk into the clinic, and difficulty with providing informed consent.

From November 2009 to March 2010, a total of 164 hypertensive patients with carotid atherosclerosis aged 56–79 (mean: 66.23 ± 6.50) years were eligible enrolled in Jinan area of Shandong Province, China. Among them, 80 were males and 84 were females. This study confirmed to good clinical practice guidelines and was conducted in compliance with the "Declaration of Helsinki". The Research Ethics Committee of the Shandong Academy of Medical Sciences approved this study, and written informed consent was obtained from each participant.

After a 2-week washout period, the eligible patients were randomized to the administration of telmisartan placebo/rosuvastatin placebo (control group), telmisartan 40 mg/rosuvastatin placebo (telmisartan group), telmisartan placebo/rosuvastatin 20 mg (rosuvastatin group), or telmisartan 40 mg/rosuvastatin 20 mg (combination group) once daily. Hydrochlorothiazide (12.5 mg daily) was used as a basic medication in four groups because it does not exhibit anti-inflammatory effects [17,27]. Target clinic BP value was defined as less than 140/90 mmHg. Investigators titrated the daily doses to 80 mg for telmisartan if target clinic BP was not reached after 2 weeks. If clinic BP value was still uncontrolled after 2 additional weeks, hydrochlorothiazide will be doubled (25.0 mg daily). During the washout period, all patients were monitored closely, and an agreement was made that if any potential problem occurred, the treatment would be re-instated, and the patient was removed from the present study. Gratifyingly, no patient had any potential problem, such as shock, stroke, or other cardio-cerebrovascular disease during the washout period.

Clinic BP was measured by an automatic digital blood pressure monitor (HEM-7071, OMRON) at initial visit (baseline), at weekly intervals during the titration period, and at 3 months thereafter. Ultrasonography of carotid arteries, flow cytometry analysis of Th17 and Treg cells, expression levels of RORγt mRNA and Foxp3 mRNA, plasma concentrations of IL-1β, IL-2, IL-6, IL-10, IL-17, IL-23, TNF-α, TGF-β1, interferon (IFN)-γ, hsCRP, monocyte chemotactic protein (MCP)-1, and laboratory biochemical measurements were evaluated at baseline and end of trial.

2.2. Ultrasonography of carotid arteries

One experienced ultrasonographer performed all examinations and was unaware of patient's history and clinical details. Common carotid IMT was measured using high-resolution ultrasound (Vivid *i*, GE Medical Systems Ultrasound Israel Ltd.) with a handheld 7.5-MHz transducer (7.5-SPC mechanic sector transducer; GE Medical Systems Ultrasound Israel Ltd.) as described in previous studies [6,28]. Each patient was examined in the supine position with the neck extended. A region 1 cm proximal to the origin of the bulb of both the right and left common carotid arteries was identified by means of B-mode ultrasonography. Three images of each B-mode, obtained at three different angles (anterior, lateral, and medial), were recorded, digitized, and saved for subsequent analysis. IMT was defined as the distance from the leading edge of the lumen–initima interface to that of the collagen-containing upper layer of the adventitia.

2.3. Flow cytometry analysis

As previously described [6,28], overnight fasting venous blood samples were obtained using tubes containing 0.2 ml sodium heparin in all patients, and each sample was processed within 2 h. Peripheral blood mononuclear cells (PBMCs) were purified by Ficoll density gradient. Then, PBMCs were aliquoted into tubes for surface and intracellular staining. Cells were incubated at 4 °C for 20 min with Phycoerythrin (PE)-conjugated anti-human CD4 to detect Th17 cells, and incubated with peridinin chlorophyll protein (PerCP)-conjugated anti-human CD4 and fluorescein isothiocyanate (FITC)-conjugated anti-human CD25 to detect Treg cells. After surface staining, according to the manufacturer's instructions, cells were stained with FITC-conjugated anti-human IL-17A (Th17 cells) or PE-conjugated anti-human Foxp3 (Treg cells) after fixation and permeabilization. After washing with PBS, stained cells were re-suspended and analyzed with a FACSCaibur cytometer (Becton Dickinson) equipped with CellQuest software.

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