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Targeting proinflammatory cytokines, oxidative stress, TGF-β1 and STAT-3 by rosuvastatin and ubiquinone to ameliorate trastuzumab cardiotoxicity

Ahmed M. Kabel[a,b,*], Abeer A. Elkhoely[c]

[a] Pharmacology department, Faculty of Medicine, Tanta University, Tanta, Egypt
[b] Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
[c] Pharmacology and toxicology department, Faculty of Pharmacy, Helwan University, Egypt

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ABSTRACT

The aim of this study was to assess the possible modulatory effects of rosuvastatin and/or ubiquinone on trastuzumab (TRZ)-induced cardiotoxicity in mice. One hundred and twenty mice were divided into six equal groups as follows: control group; TRZ group; TRZ + carboxymethyl cellulose group; TRZ + rosuvastatin group; TRZ + Ubiquinone group and TRZ + rosuvastatin + Ubiquinone group. Serum creatine kinase (CK-MB), lactate dehydrogenase (LDH), troponin I and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) were measured. Also, tissue malondialdehyde (MDA), catalase (CAT), glutathione peroxidase (GPx), interleukin 6 (IL-6), transforming growth factor beta 1 (TGF-β1) and signal transducers and activators of transcription-3 (STAT-3) were determined. Also, echocardiography was performed. Parts of the heart were subjected to histopathological, immunohistochemical and electron microscopic examination. Administration of rosuvastatin and/or ubiquinone to TRZ-treated mice induced significant increase in tissue GPx, CAT and STAT-3 with significant decrease in serum CK-MB, LDH, troponin I, NT-pro BNP, tissue MDA, TGF-β1 and IL-6 and improved the histopathological, immunohistochemical, echocardiographic and electron microscopic changes compared to the group that received TRZ alone. These changes were significant in rosuvastatin/ubiquinone combination group compared to the use of each of these drugs alone. In conclusion, rosuvastatin/ubiquinone combination may represent a new therapeutic modality to ameliorate TRZ-induced cardiotoxicity.

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1. Introduction

Trastuzumab (TRZ) is a monoclonal antibody that is widely used nowadays to treat certain types of breast cancer [1]. TRZ is thought to bind to domain IV of the extracellular segment of the HER2/neu receptors. Cells treated with TRZ undergo arrest during the G1 phase of the cell cycle leading to reduction of cellular proliferation. It has been suggested that TRZ does not alter HER-2 expression, but downregulates activation of AKT [2]. Moreover, TRZ was reported to suppress angiogenesis both by induction of antiangiogenic factors and repression of proangiogenic factors [3]. The unregulated growth observed in cancer may be due to the proteolytic cleavage of HER2/neu receptors. TRZ has the ability to activate the tumor suppressor p27 which in turn inhibits HER2/neu ectodomain cleavage in breast cancer cells [4]. Also, TRZ was reported to induce the immune system to kill cancer cells leading to antibody-dependent cell-mediated cytotoxicity [2].

The major limiting factor of the use of TRZ in treatment of cancer is the possible development of cardiotoxicity [5]. The possible mechanisms responsible for this cardiotoxicity may include generation of reactive oxygen species (ROS) as well as increased expression of the pro-inflammatory cytokines induced by TRZ administration [6]. Moreover, TRZ was reported to downregulate neuregulin-1 (NRG-1), which is essential for the activation of cell survival pathways in the cardiomyocytes and the maintenance of cardiac function [7].

Rosuvastatin (RSV) is a member of statins, a group of drugs that is mainly used to treat cases of hypercholesterolemia and related conditions and to prevent cardiovascular disease [8]. It was reported that RSV has pleiotropic effects that may be beneficial for

* Corresponding author. El-Geish street, Faculty of medicine, Tanta University, Department of Pharmacology, Tanta, Egypt.
E-mail address: drakabel@gmail.com (A.M. Kabel).

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prevention of cardiotoxicity [9]. RSV was reported to inhibit ROS-mediated oxidative stress. This may be mediated through maintaining the balance between oxidant generation and oxidant scavenging by reducing NADPH (Nicotinamide adenine dinucleotide phosphate)-dependent production of ROS, suppressing endothelial nitric oxide synthase uncoupling and inducing the antioxidant defense mechanisms [10]. In comparison to other statins, RSV was more effective as an anti-inflammatory agent, possibly through inhibiting the expression of the inflammatory mediators such as C-reactive protein and interleukin-6 (IL-6) [11]. Moreover, .RSV has been shown to be effective in preventing left ventricular remodeling and cardiac dysfunction via normalizing pSer16-phospholamban levels as well as elevating IL-10 levels and depleting IL-6 levels independent of its lipid-lowering effect [9].

Ubiquinone (Also called coenzyme Q10) is a coenzyme that is considered as a fat-soluble substance [12]. It is present in most eukaryotic cells, mainly in the mitochondria. It is a component of the electron transport chain and participates in generation of energy in the form of ATP [13]. It is widely used for management of a variety of diseases including heart disease, Huntington's disease, male infertility, parkinson's disease, cancer, migraine headache and statin myopathy [12]. This wide range of uses was attributed to its potent antioxidant and anti-inflammatory properties. The antioxidant effects of ubiquinone are derived from its energy carrier function. Ubiquinone was reported to inhibit lipid peroxidation by preventing the production of lipid peroxyl radicals. Moreover, ubiquinone was reported to efficiently prevent the oxidation of bases mainly in the mitochondrial DNA and regenerate other antioxidants such as vitamin E [14]. The anti-inflammatory properties of ubiquinone were attributed to its ability to inhibit the expression of the proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and IL-6 [15]. The aim of this study was to assess the possible ameliorative effects of RSV and/or ubiquinone on TRZ-induced cardiotoxicity in mice and to explore the possible molecular mechanisms of these effects.

2. Materials and methods

2.1. Drugs and chemicals used

TRZ (Herceptin) and isotype IgG antibody were supplied by Genentech (San Francisco, CA, USA) and dissolved in sterile distilled water. RSV was supplied by AstraZeneca Pharmaceuticals LP. Ubiquinone (Coenzyme Q10) was supplied by Medicines Pvt. Ltd. (Mumbai, India). Carboxymethyl cellulose (CMC) was obtained from Sigma Pharmaceutical Company, Quesna, Egypt. Both RSV and ubiquinone were suspended in 0.5% CMC solution. All other chemicals were purchased from Sigma Aldrich Co., USA.

2.2. Classification of animals

In this study, we used one hundred and twenty male Balb/c mice weighing about 20–25 grams obtained from the animal house of the faculty of medicine, Tanta University, Egypt. They were allowed to acclimatize for two weeks before starting the experiment. The animals were kept in a special room at a constant temperature of 25 ± 3 °C with relative humidity of $60 \pm 10\%$, exposed to 12 h light/dark cycles with free access to food and tap water. All the experiments were conducted according to the National Research Council's guidelines. Animal handling was followed according to Helsinki declaration of animal ethics. The animals were randomly divided into six equal groups as follows:

Group (1): The control group; received intraperitoneal injection of isotype IgG antibody in a dose of 4 mg/kg once weekly for 5 weeks [16].

Group (2): TRZ was given by intraperitoneal injection in a dose of 4 mg/kg once weekly for 5 weeks [17].

Group (3): Received 0.5% CMC solution daily by oral gavage two weeks before and continued for 5 weeks after starting administration of TRZ.

Group (4): Received RSV in a dose of 40 mg/kg body weight daily by oral gavage two weeks before and continued for 5 weeks after starting administration of TRZ [18].

Group (5): Received ubiquinone in a dose of 200 mg/kg body weight daily by oral gavage two weeks before and continued for 5 weeks after starting administration of TRZ [19].

Group (6): Received RSV in a dose of 40 mg/kg body weight daily by oral gavage concomitantly with ubiquinone in a dose of 200 mg/kg body weight daily by oral gavage two weeks before and continued for 5 weeks after starting administration of TRZ.

2.3. Assay of the biochemical parameters

At the end of the study (24 hours after the last treatment), mice were anaesthetized using 50 mg/kg pentobarbital sodium given by intraperitoneal injection, followed by blood collection from the retro-orbital plexus. The collected blood was centrifuged at 5000 rpm for 10 minutes, sera were collected and stored at −30 °C for determination of serum lactate dehydrogenase (LDH) according to Buhl and Jackson [20], serum creatine kinase (CK-MB) according to Hess et al. [21] and serum troponin I using ELISA kits obtained from Sigma Aldrich Co. according to the instructions of the manufacturer. Serum N-terminal pro-B-type natriuretic peptide (NT-pro BNP) levels were analyzed (K2-EDTA anticoagulated whole blood) using time resolved florescence assay on AQT90 FLEX immunoassay analyzer (Radiometer, DK) and reported in ng/L.

Then, all mice were sacrificed and the hearts were extracted. Parts of the cardiac tissues were homogenized for determination of cardiac catalase (CAT) according to Abei method [22], cardiac malondialdehyde (MDA) according to Lima et al. [23], cardiac glutathione peroxidase (GPx) using BIOXYTECH GPx-340TM Assay kit produced by OXIS International, Inc., USA according to Rotruck et al. [24], cardiac interleukin-6 (IL-6) using mouse ELISA kits supplied by RayBiotech, Inc., USA according to the instructions of the manufacturer, cardiac transforming growth factor beta 1 (TGF-β1) using Boster immunoleader ELISA kit supplied by R&D systems, USA according to the manufacturer's instructions, and cardiac signal transducers and activators of transcription-3 (STAT-3) levels using ELISA kits supplied by RayBiotech, Inc., USA according to the manufacturer's instructions.

2.4. Murine echocardiography

In vivo cardiac function was evaluated by murine echocardiography, as described by Walker et al. [25]. Awake mice were imaged at baseline and at the end of the study. Images were captured in M-mode using a 13-MHz linear array ultrasound probe (Vivid 7, GE Medical Systems, Milwaukee, WI, USA). M-mode recordings were used to evaluate indices of cardiac dimensions and functions including left ventricular end diastolic internal diameter (LVID), posterior wall thickness (PWT), LV fractional shortening (LVFS) and LV ejection fraction (LVEF).

2.5. Histopathological and immunohistochemical examination

2.5.1. Hematoxylin and eosin (H & E) staining of the cardiac tissues

The cardiac sections were deparaffinized by using xylene, hydrated in alcohol, stained with hematoxylin for 10 minutes and then counterstained with 1% eosin solution. Then, sections were dehydrated and mounted in Canada balsam [26].

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