Efficacy of Telmisartan Versus Dexamethasone on Induced Bronchial Asthma in Experimental Rat

Original Article

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ABSTRACT

Background: Bronchial asthma is a progressive and disability disease. Most treatment lines of bronchial asthma still act as bronchodilators and anti-inflammatory drugs rather than treating underlying disease pathogenesis so new drug classes are needed to be tested as primary goals. Angiotensin II is potentially implicated in its pathogenesis, being a potent pro-inflammatory mediator with remodeling effects.

Aim: To study potential beneficial effect of telmisartan, an angiotensin II receptor blocker, on experimentally induced bronchial asthma in rats.

Patients and Methods: 30 male Sprague Dawley rats were divided into 5 groups; a normal control group, an asthma control group, a dexamethasone treated group, telmisartan treated groups and salbutamol treated group. Bronchial asthma was induced by intraperitoneal sensitization followed by intranasal challenge with ovalbumin (OVA). PULMONARY function tests were assessed 1 h after the last challenge. One day after the last challenge, absolute eosinophil counts (AEC) in blood and bronchoalveolar lavage fluids (BALF), Serum and BALF immunoglobulin E, total nitrate/nitrite (NOx), Oxidative and inflammatory biomarkers, lung tissue superoxide dismutase (SOD), glutathione reduced (GSH), tumor necrosis factor-alpha (TNF-a) and interleukin-5 (IL-5), were assessed, in addition to histopathological study.

Results: Telmisartan significantly improved TV, PEF, AEC, IgE, NOx, GSH, SOD, TNF-a and IL-5 values compared to asthma control values. Histopathological study runs in parallel to biochemical results showing normal lung architecture in telmisartan treatment.

Relation between patient's results and types of graft used showed no statistically significant differences between them.

Conclusion: These results shows that telmisartan ameliorate bronchial asthma as regarding biochemicals and histological results due to its bronchodilator, antioxidant, and anti-inflammatory effects.

Key Words: Airway remodeling, bronchial asthma, dexamethasone, telmisartan.

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INTRODUCTION

Bronchial asthma is a progressive and disability disease. The prevalence of bronchial asthma increases worldwide about 50% every decade., and this number would increase as countries became more civilian [1] as treatment depends only on bronchodilator and anti-inflammatory which do not achieve our targets, We try to cover overall and all possible and available lines of therapy.

Bronchial asthma is a chronic airway inflammation in which there is increased infiltration of eosinophils, mast cells and activated T-helper lymphocytes that cause production of various cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (ILs). These inflammatory mediators aggravate airway obstruction, mucus secretion and produce airway remodeling [2]. in addition, reactive oxygen species (ROS) production increases. Most treatment lines of bronchial asthma still act as bronchodilators and anti-inflammatory drugs rather than treating underlying disease pathogenesis [3] so new drug classes are needed to be tested as primary goals.

Angiotensin II produced from the renin angiotensin aldosterone system (RAAS), is formed from angiotensin I by the angiotensin converting enzyme (ACE) that is highly expressed in the lungs [4].

angiotensin II is a potent vasoconstrictor and a potent pro-inflammatory mediator that promote growth and remodeling effects. Numerous studies have proven that interruption of RAAS system significantly reduced ROS production and inflammatory progression by reducing proinflammatory mediators in animal models [5].

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Angiotensin II has two receptor angiotensin II type 1 (AT1) and angiotensin II type 2 (AT2) receptors. numerous studies have documented that angiotensin II-induced bronchoconstriction (AT1 receptor) and production of leukotrienes in guinea pigs [6]. The potentiating effect of angiotensin II on endothelin-1-induced contraction of bovine bronchial smooth muscle was also reported [7].

Several mechanisms have been suggested to the process of bronchial asthma the airway hyperresponsiveness, abnormality of the nature of airway smooth muscle. augmented airway smooth muscle contraction in the airway obstruction. So another line therapy of bronchial asthma is understanding contractile signaling of airway [8].

Smooth muscle contraction is mainly regulated by Calcium concentration in myocytes. But Recently, an additional mechanism, termed Calcium sensitization, has also been explained in smooth myocytes [7].

Although pathogenesis is not fully understood, there is increasing evidence that a RhoA and its downstream target Rho-kinase are involved in Calcium sensitization of airway smooth muscle contraction [6-8] Recent studies revealed an augmentation of the RhoA/Rho-kinase–mediated Ca2+ sensitization in diseased smooth muscles such as coronary and cerebral vasospasms and hypertension. It is possible that an augmentation of the RhoA/Rho-kinase system might be one of the causes of the bronchial smooth muscle hyperresponsiveness [9].

Glucocorticoids are the most effective therapy of bronchial asthma. It acts primarily as anti-inflammatory agents however Recent studies have also demonstrated that glucocorticoids effect go beyond its anti-inflammatory action and may involve glucocorticoid receptors [10-12].

Telmisartan acts as a partial agonist on the nuclear peroxisome proliferator-activated receptor-gamma (PPAR-γ) that has anti-oxidative and anti-inflammatory effects [13]. Accordingly to study on mouse model of bronchial asthma activation of PPAR-γ inhibit eosinophilia in the lung [7].

The present study aims to investigate the possible protective effect of telmisartan on bronchial asthma induced experimentally in rats and compare to the standard anti-asthmatic drug dexamethasone (DEXA) and salbutamol.

PATIENTS AND METHODS:

ANIMALS

A total of 30 male sprague Dawely Albino rats, weighing 200-250 g were used in this study (Purchased from animal house, research institute of ophthalmology, Giza, Egypt). All rats were housed in a room at a constant temperature of 23 ± 10C, humidity of 60% ± 10%, and a 12 hr light/dark cycle. The animals were housed in groups and kept at constant nutritional conditions throughout the experimental period. All experiments were from housed for the 1st week of the study for acommodation the 2nd week.

Chemicals, Drugs and Reagent Kits

Ovalbumin (OVA) and aluminum hydroxide (Al(OH)3): Sigma Aldrich Chemical Co. (St. Louis, MO, USA).

Telmisartan and DEXA: Sigma Aldrich Chemicals Co., Egypt.

IgE ELISA kit; TNF-a ELISA kit and IL-5 ELISA kit: Sigma Aldrich Chemical Co. (St. Louis, MO, USA).

Experimental Design

30 Rats were divided into 5 groups, each of 6 rats. Test agents or vehicles will be administered orally on a daily basis for 14 days prior to OVA challenge and during the challenge days.

GROUP I: NORMAL CONTROL, received only vehicles.

GROUP II ASTHMA CONTROL sensitized and challenged with OVA and kept as asthma control.

GROUP III: DEXA GROUP: sensitized and challenged with OVA and: received DEXA as reference drug, in a dose of 1 mg/kg/day intramusculary. Og (oral gavage).

GROUPS IV: TELMISARTAN GROUP: sensitized and challenged with OVA and received telmisartan in dose10 mg/kg/day.

GROUP V: SALBUTAMOL GROUP: sensitized and challenged with OVA the salbutamol group treated subcutaneously with 1 mg kg-’ body weight of salbutamol m 0 9% NaCl solution.

Rats will be weighed at the beginning and end of the experiment.

METHODS

INDUCTION OF BRONCHIAL ASTHMA

Sensitization with OVA

Ovalbumin was prepared in a concentration of 400 µg/ml in saline and precipitated with Al(OH)3 (20 mg/ml) solution at 1:1 ratio. Rats were sensitized

with an intraperitoneal injection of 200 µg OVA/10 mg Al(OH)3 (1 ml suspension) at days 1, 2, 3 and 11 according to manufacture instuction [13].

Intranasal challenge with OVA

At day 20, rats were anesthetized with isoflurane, and 300 µl of saline containing 1.5 mg of OVA was instilled into both airways of nasal cavity for 3 consecutive days. The instillation method was carried out according to manufacture instuction [14].

Pulmonary functions test:

Measurement of tidal volume (TV) and peak expiratory flow (PEF):

Assessment of pulmonary function was made 1 h after the last challenge. For measurement of TV and PEF, non anesthesized rats were placed in the main chamber of the whole body plethysmograph. Rat heads were protruded into a chamber connected to a spirometer according to previous described methods [10].

Measurement of seum IgE:

Blood samples were collected from the retro-orbital plexus vein. Samples were left to clot at room temperature then centrifuged at 2000 rpm for 10 min for serum separation. Serum samples were stored at -200 C for estimation of IgE level [11].

Bronchoalveolar lavage fluid (BALF) collection

Animals were sacrificed by cervical dislocation, BALF was collected by lavaging the lungs with two aliquots of 5 ml of ice-cooled normal saline. Total collected volume per rat was approximately 8 ml. BALF was centrifuged at 400 rpm for 10 min at 40C, supernatant liquid was stored at 800 C until estimation of total nitrate/nitrite (NOx). Cellular pellets were resuspended in 50 µl of phosphate buffered saline [15] for absolute eosinophils count (AEC) in the pellets.

Preparation of Lungs

The two lungs were dissected, washed from blood by ice-cooled saline, blotted with a piece of filter paper and weighted separately. The left lung was used for histopathological examination while the right lung was homogenized in ice-cooled saline to prepare 25% w/v homogenate using a homogenizer. Lung homogenates were centrifuged at 2000 rpm for 20 min at 4oC, then stored at -80oC for further biochemical analysis of glutathione reduced (GSH), superoxide dismutase SOD), TNF-α and interleukin-5 (IL-5).

Biochemical Measurements

Serum IgE was determined by ELISA according to the manufacturer's instructions.

The absolute eosinophil count (AEC) was measured in the pellets within 1 h in BALF [12].

NOx content: was estimated in BALF according to the method described earlier.

The oxidative stress markers GSH and SOD: were estimated in lung homogenates by methods previously described.

Lung tissue levels of TNF-a and IL-5: were determined using ELISA kits according to the manufacturer's instructions [6-21].

Histopathological study

Left lungs of all animals were dissected immediately after sacrifice, washed with saline, and fixed in 10% formalin solution in saline for 72 h. Paraffin sections, 5 µm thick were prepared by conventional methods. Paraffin sections were stained with hematoxylin and eosin (H&E) stain [22]. Perivascular and peribronchiolar inflammation scores were determined for 3 rats per group, giving score 0 to normal sections, score 1 for presence of few inflammatory cells, score 2 for a ring of inflammatory cells one cell layer deep, score 3 for a ring of inflammatory cells two to four cells deep, and score 4 for a ring of inflammatory cells of more than four cells deep [23].

STATISTICAL ANALYSIS:

All collected questionnaires were revised for completeness and consistency. Pre-coded data was entered on the computer using "Microsoft Office Excel Software" program (2010) for windows. Data was transferred to the Statistical Package of Social Science Software program, version 24 (SPSS) to be statistically analyzed.

Data was summarized using mean, and standard deviation for quantitative variables and frequency and percentage for qualitative ones.

Comparison between groups was performed using one way ANOVA with Tukey's post hoc test for quantitative variables and Chi square or Fissure exact test for qualitative ones.

P values less than 0.05 were considered statistically significant, and less than 0.01 were considered highly significant.

RESULTS:

Group I :Normal Control, Received Only Vehicles

Pulmonary function test within normal range. (Table 1).

Blood and BALF pellets AEC within normal range. (Table 2).

Serum IgE and BALF NOx within control mean value. (Table 3).

GSH and SOD levels in lung homogenate within control mean value (Table 4). within control mean value (Table 5). TNF-a and IL-5 levels in lung homogenate.

Histopathological study: Light microscopic examination of the lung tissue sections obtained from normal rats showed normal architecture of lung tissue, bronchioles and alveoli (Fig. 1).

Perivascular and peribronchiolar score (Table 6).

Group II: Sensitized and Challenged with Ova and Kept as Asthma Control

Pulmonary function tests: Intsranasal OVA challenge significantly decreased both TV and PEF to 5550% and 600% respecively, as compared to the normal control group. (Table 1).

Blood and BALF pellets AEC: Intranasal OVA challenge significantly increased blood and BALF pellets AEC to 200% and 1800%, respectively, as compared to the normal control group. (Table 2).

Serum IgE and BALF NOx: Intranasal OVA challenge significantly increased IgE in serum and NOx in BALF to reach 1560% and 240%, respectively, as compared to the normal control group. (Table 3).

GSH and SOD levels in lung homogenate: Intranasal OVA challenge significantly reduced lung GSH level and SOD activity to 26% and 16%, respectively, as compared to normal control group (Table 4).

TNF-a and IL-5 levels in lung homogenate: Intranasal OVA challenge significantly increased lung TNF-a and IL-5 levels to 700% and 500%, respectively, as compared to normal control group. (Table 5).

Histopathological study: Light microscopic examination of the lung tissue sections from rats subjected to OVA-induced bronchial asthma showed severe inflammatory infiltrates and distorted bronchial and alveolar architectures (Fig. 2).

Perivascular and peribronchiolar score (Table 6).

Group III: Dexa Group: Sensitized and Challenged with Ova and: Received Dexa as Reference Drug, in A Dose of 1 Mg/Kg/Day Og

Pulmonary function tests: Administration of DEXA increased TV and PEF to reach, respectively, as compared to asthma control group (Table 1) 50% and 560 550%.

Administration of DEXA significantly decreased AEC in blood and BALF pellets to 60% and 13%, respectively, as compared to asthma control group (Table 2).

Serum IgE and BALF NOx: Administration of DEXA significantly decreased serum IgE and BALF NOx levels, reaching about 14% and 60%, respectively, of the asthma control mean values. (Table 3).

GSH and SOD levels in lung homogenate: Administration of DEXA significantly increased lung GSH level and lung SOD activity to 430% and 200%, respectively, as compared to asthma control group. (Table 4).

TNF-a and IL-5 levels in lung homogenate: Administration of DEXA significantly decreased both lung TNF-a and IL-5 levels to about 300 and 319% respecively, as compared to asthma control group. (Table 5).

Histopathological study:

Light microscopic Lung sections obtained from rats subjected to OVA-induced bronchial asthma and pretreated with DEXA showed normal lung architecture and mild inflammatory infiltration (Fig. 3).

Perivascular and peribronchiolar score (Table 6).

Groups IV: telmisartan group: sensitized and challenged with OVAand received telmisartan in dose10 mg/kg/day.

Pulmonary function tests: Administration of telmisartan significantly increased TV to 555%, and increased PEF to 590%, as compared to asthma control group (Table 1).

Blood and BALF pellets AEC: Administration of telmisartan significantly decreased AEC in blood to 25%, and in BALF pellets to 85%, as compared to asthma control group (Table 2).

Serum IgE and BALF NOx: Administration of telmisartan significantly decreased serum IgE level to

280%, (Fig. 3), while significantly decreased BALF NOx 45%, as compared to asthma control group (Table 3).

GSH and SOD levels in lung homogenate: Administration of telmisartan significantly increased lung GSH level to 420%, , and significantly increased lung SOD activity to 170%, as compared to asthma control group (Table 4).

TNF-a and IL-5 levels in lung homogenate: Administration of telmisartan significantly decreased lung TNF-a level to 22%, , and significantly decreased lung IL-5 level to 313% and 583% respecively, as compared to asthma control group (Table 5).

Histopathological study:

Light microscopic examination of the lung tissue sections obtained from rats subjected to OVA-induced bronchial asthma and pretreated with telmisartan (10 mg/ kg), showed mild inflammatory reaction in the peribronchiolar and perivascular regions (Fig. 4).

Perivascular and peribronchiolar score (Table 6).

Group V: Salbutamol Group: Sensitized and Challenged With Ova The Salbutamol Group Treated Subcutaneously With 1 Mg Kg-' Body Weight of Salbutamol M 0 9% Nacl Solution

Pulmaonary function tests: Administration of salbutamol significantly increased TV to 550% and increased PEF to 600% , as compared to asthma control group (Table 1).

Blood and BALF pellets AEC: Administration of salbutamol significantly decreased AEC in blood to 60%, and in BALF pellets to 52% as compared to asthma control group (Table 3).

Serum IgE and BALF NOx: Administration of salbutamol significantly decreased serum IgE level to 78% (Fig. 3), while significantly decreased BALF NOx content to 70%, as compared to asthma control group (Table 4).

GSH and SOD levels in lung homogenate: Administration of salbutamol significantly increased lung GSH level to 378% and significantly increased lung SOD activity to 155%, as compared to asthma control group (Table 4).

TNF-a and IL-5 levels in lung homogenate: Administration of salbutamol significantly decreased lung TNF-a level to 50%, and significantly decreased lung IL-5 level to 60%, as compared to asthma control group (Table 5).

Histopathological study:

Light microscopic examination of the lung tissue sections obtained from rats subjected to OVA-induced bronchial asthma and pretreated with salbutamol, showed mild to moderate inflammatory reaction mainly in the peribronchiolar andperivascular regions (Fig. 5).

Perivascular and peribronchiolar score (Table 6).

Table 1: Tidal volume (TV) and peak expiratory flow (PEF)

Group	TV (ml)	PEF (ml/min)
I (normal control)	0.1±0.004	12±0.3
II (Ashma control)	0.018±0.003*	2.04±0.27*
III Dexa	0.93±0.001**	11.45±0.08**
IV Telmisartan	0.1±0.005**	11.7±0.23**
V Sabutamol	0. 0.002**	12±0.89**

* denotes signicant diffence from normal control group (*p value < 0.05*)
** denotes signicant diffence from asthma control group (*p value < 0.05*)

Table 2: (A) absolute eosinophil count (AEC) in the blood samples, (B) absolute eosinophil count (AEC) in pellets of BALF in asthmatic rats

Group	Blood AEC	Pellets AEC
I (normal control)	100±20	70±10
II (Ashma control)	190± 20*	1700 ±120*
III Dexa	110±30**	220±40**
IV Telmisartan	40±10**	200±30**
V Sabutamol	130±20**	900 ±180**

* denotes signicant diffence from normal control group (*p value < 0.05*)
** denotes signicant diffence from asthma control group (*p value < 0.05*)

Table 3: Serum IgE level in asthmatic rats and total nitrate/nitrite (NOx) in bronchoalveolar lavage fluid (BALF).

Group	Seum Ig E	BALF NO_x
I (normal control)	40±10	40±4
II (Ashma control)	1400± 200*	80±6*
III Dexa	60±20**	45±4**
IV Telmisartan	50± 10**	39±4**
V Sabutamol	1100±150**	30±5**

* denotes signicant diffence from normal control group (*p value < 0.05*)
** denotes signicant diffence from asthma control group (*p value < 0.05*)

Table 4: Lung glutathione reduced (GSH) level and superoxide dismutase (SOD) activity

Group	GSH (µg/g tissue)	SOD (IU/g tissue)
I (normal control)	190±2	25.3±0.9
II (Ashma control)	49.4±9.3*	15.7±1.6*
III Dexa	201±14.2**	29±3.3**
IV Telmisartan	198± 13**	26.31±2.9**
V Sabutamol	170± 9.3**	16.71±3.4**

* denotes signicant diffence from normal control group (*p value < 0.05*)
** denotes signicant diffence from asthma control group (*p value < 0.05*)

Table 5: Lung content of TNF-α, and lung content of IL-5 in asthmatic rats

Group	Lung TNF-α	Lung IL-5
I (normal control)	10010±	909±
II (Ashma control)	70040± *	47020± *
III Dexa	20010± **	13010± **
IV Telmisartan	12030± **	15020± **
V Sabutamol	40050± **	20030± **

* denotes signicant diffence from normal control group (*p value < 0.05*)
** denotes signicant diffence from asthma control group (*p value < 0.05*)

Table 6: Perivascular and peribronchiolar inflammation score was performed as described before. Three rats per group were analyzed

	Perivascular					peribronchiolar				
	Score 0	I	II	III	IV	Score 0	I	II	III	IV
I (normal control)	2	1	0	0	0	2	1	0	0	0
II (Ashma control)*	0	0	0	1	2	0	0	0	1	2
III Dexa**	2	1	0	0	0	2	1	0	0	0
IV Telmisartan**	0	2	1	0	0	1	2	0	0	0
V Sabutamol**	0	1	1	1	0	0	1	1	1	0

* denotes signicant diffence from normal control group (*p value < 0.05*)
** denotes signicant diffence from asthma control group (*p value < 0.05*)

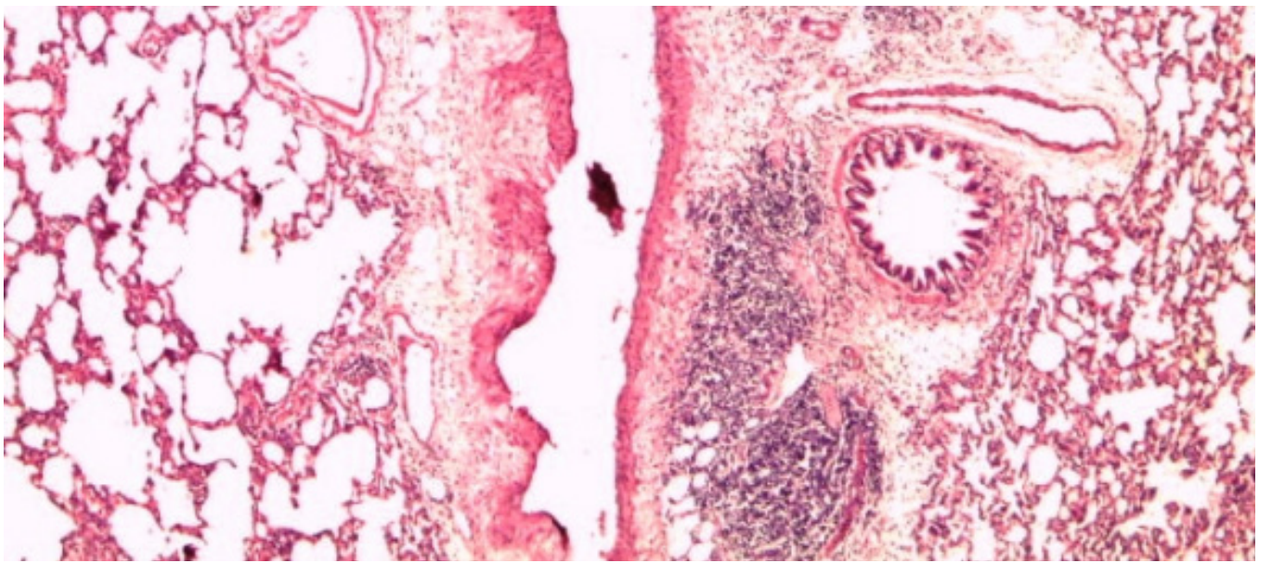

Fig. 1: Normal control group: photomicrographs of lung sections obtained from normal animals, showing normal architecture of lung tissue, bronchioles and alveoli. Absence of inflammatory cells infiltrates [(H&E 100x)].

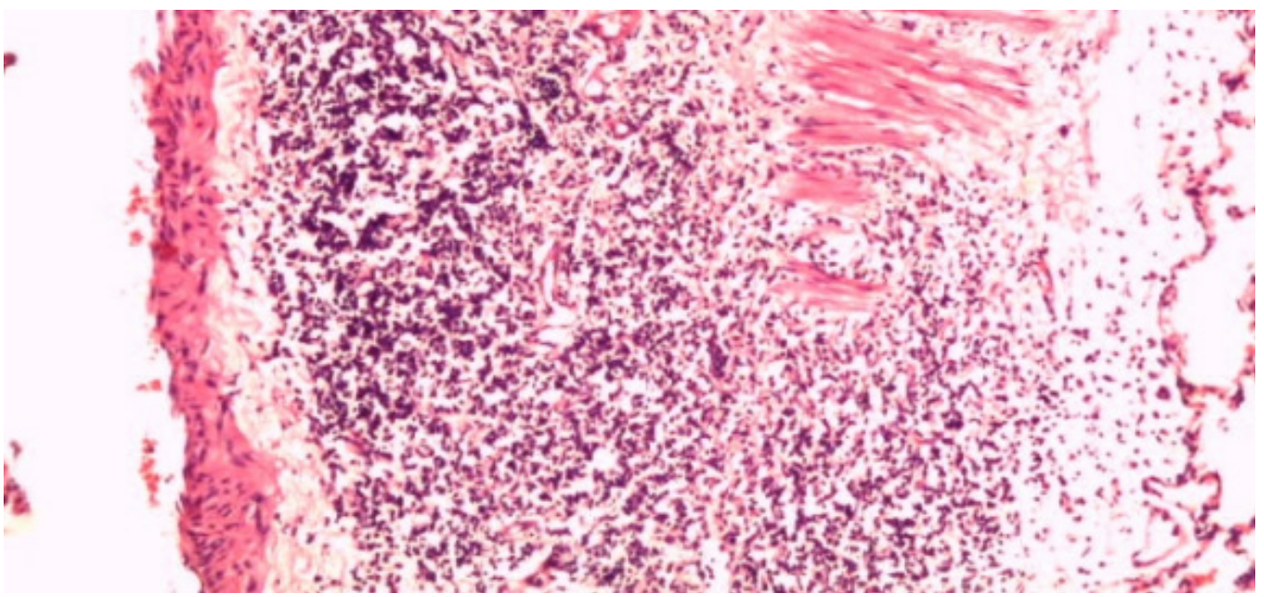

Fig. 2: Bronchial asthma control group: showing severe inflammatory infiltrates and distorted bronchial and alveolar architectures [H&E 200x].

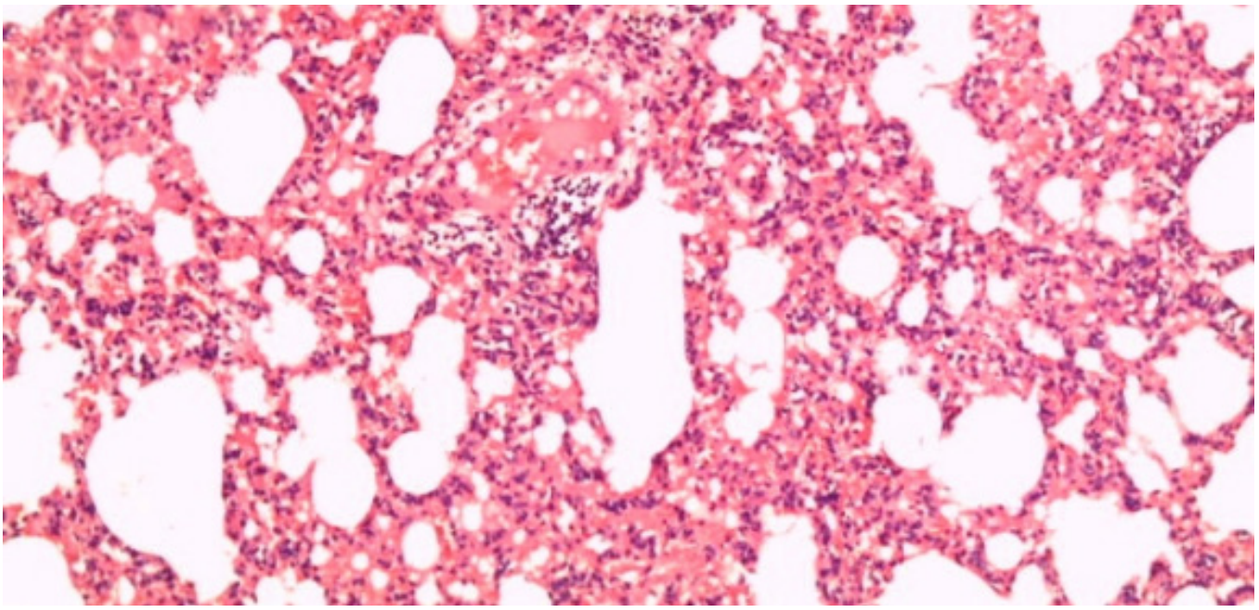

Fig. 3: Dexamethasone (reference) treatment group: showing normal lung architecture and very mild inflammatory cell infiltration [H&E 200x].

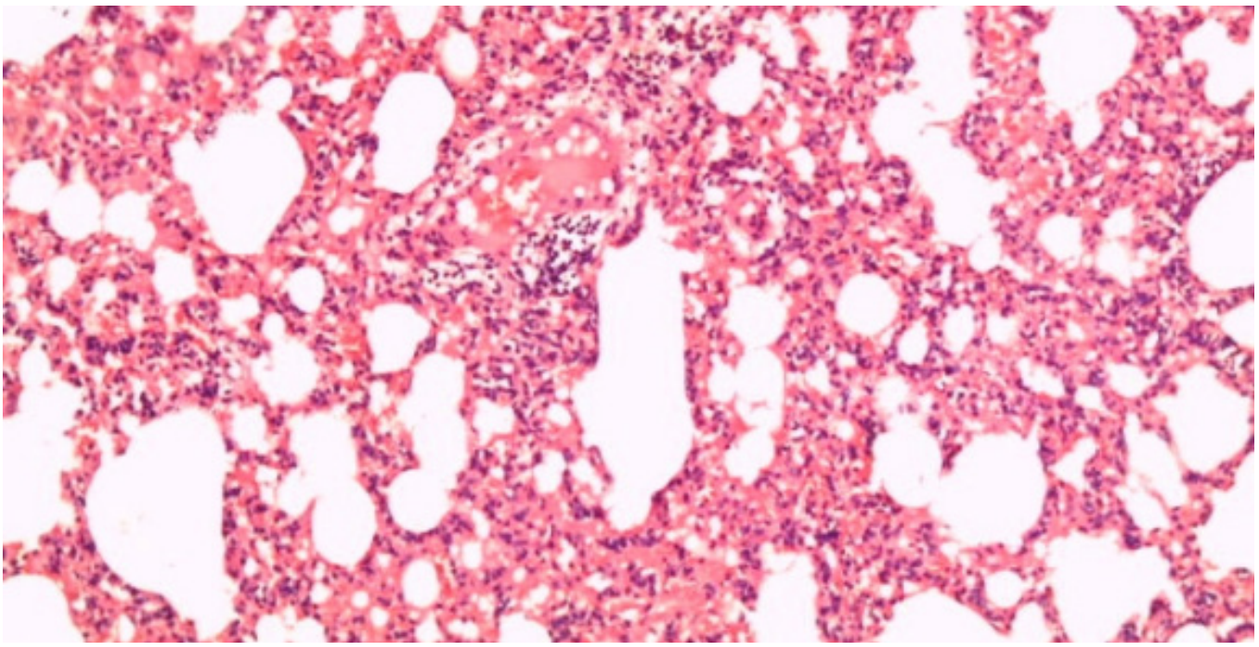

Fig. 4: Telmisartan treatment group: showing mild inflammatory reaction in the peribronchiolar and perivascular regions [(H&E 200x].

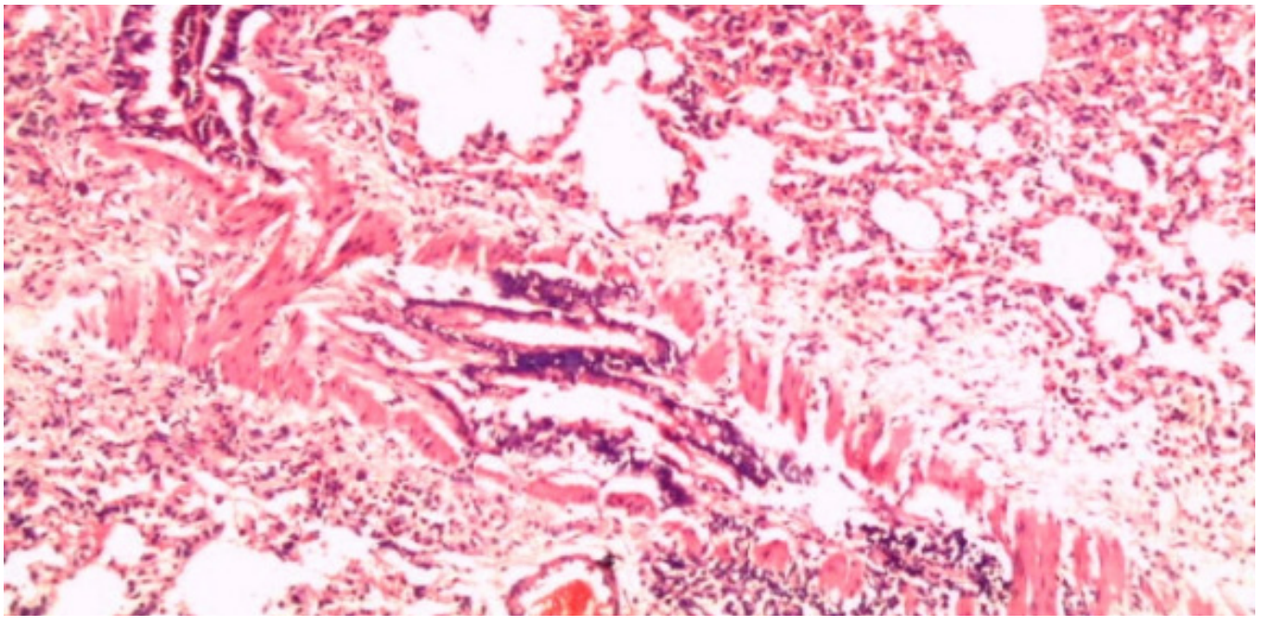

Fig. 5: Salbutamol treatment group: showing moderate inflammatory cell infiltration mainly in the peribronchiolar and perivascular regions [(H&E 100x].

DISCUSSION

In our study, WE studied beneficial effect of telmisartan, and we compared it to the reference anti-asthmatic drug DEXA and salbutamol, was investigated on OVA-induced bronchial asthma in experimental rats.

Results of our study showed that OVA challenge in sensitized rats significantly decreased the pulmonary function tests as compared to normal control rats, indicating bronchoconstriction [23,24]. Administration of DEXA significantly improved TV and PEF [24,25-27]. Administration of telmisartan significantly attenuated OVA-induced bronchoconstriction as compared to asthma control group. In agreement with Watanabe *et al*. 2004 showed that AT1 receptors are incorporated in angiotensin II-induced bronchoconstriction in guinea pigs [26-28] and production of leukotriene in guinea pig airways, which was attributed to the potentiating effect of angiotensin II on endothelin-1-induced contraction of bovine bronchial smooth muscle [27]. Salbutamol administration improved pulmonary function tests.

Our study revealed that OVA challenge significantly increased airways eosinophils infiltration [29-30]. DEXA significantly decreased absolute eosinophil count in blood and in BALF as compared to asthma control animals, as DEXA has the ability to suppress the production and secretion of eotaxin in airway epithelial cells [31]. Telmisartan, due to its partial agonistic activity on the nuclear PPAR-γ, significantly reduced OVA-induced increase in blood and BALF eosinophils [7].

Serum IgE level in our study significantly increased in asthma control group [31,32]. DEXA prevent OVA-induced increase in serum IgE level [9]. Additionally, ARBs were reported to suppress antigen-specific type-1T-helper cell (Th1) responses in vivo [9].

This study showed that OVA challenge significantly increased NOx content in BALF [32,33] suggesting that NO is an inflammatory marker and a cytotoxic molecule contributing to epithelial damage. it is known that ROS production plays an important role in the pathogenesis and progression of asthma. In this study, OVA significantly increased ROS generation as decreased lung GSH level and SOD activity. Such ROS may contribute to tissue injury and inflammatory reactions. DEXA administration significantly decreased NOx content in BALF and significantly increased GSH level and SOD activity in lung homogenate as compared to asthma control rats, [34].

Telmisartan is the only angiotensin-II type 1 antagonists that acts as a selective PPAR-γ receptor modulator having anti-oxidative and anti-inflammatory effects. Also, PPAR-g inhibits the secretion of inducible NO synthase which is involved in tissue damage [13-35]. This study supports practically the previous data as telmisartan administration significantly reduced NOx content in BALF and significantly increased GSH level and SOD activity in lung tissue.

In this study, OVA challenge significantly increased lung tissue levels of TNF-α and IL-5, the pro-inflammatory cytokines [10]. TNF-α activates nuclear factor kappa (NF-kß) that crosses the nuclear membrane and activates several genes which are responsible for synthesis of prostaglandin G2 leading to inflammation [36,37]. IL-5 is an important cytokine that plays a central role in eosinophil maturation in bone marrow, and then migrates to the blood in the late-phase response to antigen challenge [38]. DEXA administration significantly decreased TNF-α and IL-5 levels in lung homogenate as compared to asthma control animals [39,40], telmisartan administration exerted anti-inflammatory effects by decreasing production of TNF-a and IL-5 in lung tissue when compared with asthma control group.

Histopathological study. Administration of DEXA showed mild inflammatory infiltration and normal lung architecture [10]. Telmisartan administration showed very mild inflammation and nearly normal epithelium lining. These findings strongly support results of biochemical markers [41].

The anti-inflammatory effect of telmisartan in addition to effective PPAR-γ activation are beneficial in bronchial asthma.

CONFLICT OF INTEREST

There are no conflicts of interest.

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