Original Article

Disease modifying effects of Simvastatin &/or Telmisartan on pulmonary function in patients with mild to moderate chronic obstructive pulmonary disease (COPD)

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Summary:

Background: Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and a range of pathological changes in the lung, some significant extra-pulmonary effects, and important comorbidities which may contribute to the severity of the disease in individual patients. Many immune, inflammatory and oxidative stress markers were found to be involved in the pathogenesis of COPD and inhibition of which was related to improved pulmonary function in these patients.

Objective: The aim of this study is to evaluate the anti-inflammatory, antioxidant and immunomodulatory effects of simvastatin, telmisartan or their combination on pulmonary function in patients with COPD.

Subjects and methods: Eighty patients with mild to moderate COPD according to GOLD standards criteria were participated in this study. They were recruited into four groups where the first group includes 20 patients on an inhaled β2- agonist only (control), the second group includes 20 patients on an inhaled β2- agonist plus 20mg/d simvastatin, the third group includes 20 patients on an inhaled β2- agonist plus 40mg/d telmisartan and the fourth group includes 20 patients on an inhaled β2- agonist plus combination of both simvastatin and telmisartan. Twenty apparently healthy subjects were selected to be a normal group for comparison. Baseline , 3 and 6 months periods were used to monitor patients. Pulmonary function tests were measured by a spirometer (spirolab III) as forced expiratory volume in the first second (FEV1), forced expiatory flow at 25-75% of the forced vital capacity (FEF25-75%), peak expiratory flow (PEF) and forced expiratory volume in the third second (FEV3). In addition, assessing the plasma levels of tumor necrosis factor alpha (TNF-α), malonyl dialdehyde (MDA) as markers of inflammation and oxidative stress was performed. ANOVA method for statistics was used to compare the results.

Results: The results showed that treatment with simvastatin, telmisartan and combination of both was associated with improved pulmonary outcomes by affecting the inflammatory and oxidative stress processes and this indicated by improvement in FEV1, FEF25-75%, PEF and FEV3, and reduction of TNF-α and MDA. However, the most effective therapy was with the combination of both simvastatin and telmisartan.

Conclusion: The anti-inflammatory, antioxidant effects of simvastatin and telmisartan were associated with improved pulmonary function and there may be a potentiation effect between statins and angiotensin receptor blockers (ARBs) that require further approval.

Key words: Statins, Angiotensin receptor blockers, COPD.

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Introduction:

Chronic obstructive pulmonary disease (COPD), a condition characterized by airway limitation, inflammation, and long-term lung function decline, is a leading cause of mortality in the United States and the world (1). In COPD, airway pro-inflammatory cytokine levels have been demonstrated to be associated with increased airway obstruction and exaggerated airway inflammatory response (2, 3). Oxidative stress, an imbalance between oxidants and antioxidants, is increased in patients with COPD, particularly during exacerbations, and reactive oxygen species contribute to its pathophysiology (4, 5). Reduction in oxidative stress in patients with COPD should provide clinical benefit through reducing inflammation (6).

Recently statins have emerged as a possible disease modifying agent in COPD. The rationale for this at least partly derives from the fact that the pathogenesis of COPD involves inflammatory processes (10), and persistent systemic inflammation seems to be present even in patients with stable COPD who do not currently smoke (7). Studies have also demonstrated that statins reduce oxidative stress (8). Inflammation is considered central to the pathogenesis of COPD and oxidative stress is also believed to be important in its development (9). The Angiotensin-converting enzyme (ACE) is highly expressed in lungs, where it degrades bradykinin and catalyses the formation of the Angiotensin II (AII); a powerful vasoconstrictor, inflammatory modulator and cellular growth factor.

There have been several recent pharmacoepidemiologic studies that have demonstrated that statin and/or ACE inhibitor

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use were associated with improved outcomes for patients hospitalized with acute COPD exacerbations or for those with pre-existing COPD (10).

Subjects & methods:

This study was carried out at Al- Basra General Hospital from December 2009 until June 2011. Eighty patients were participated in this study where they have been grouped into four groups. The first group involved 20 COPD patients on salbutamol inhaler only 200-800 microgram daily as required (control). The second group involved 20 COPD patients on salbutamol inhaler plus simvastatin 20mg/d. The third group involved 20 COPD patients on salbutamol inhaler plus telmisartan 40mg/d. The fourth group involved 20 COPD patients on salbutamol inhaler plus combination of both simvastatin and telmisartan. Twenty apparently healthy subjects were selected to participate as a normal group for comparison, they were 16 males (80%) and 4 females (20%). The mean age of these subjects was (59.09 ± 8.71). The age of patients ranged from 40 – 65 years (Mean ± SD 58.8 ± 9.1). They, 64 patients (80%) male and 16 patients (20%) female. Diagnosis was made by a specialized physician in internal medicine for patients as having COPD depending on patient history, clinical examination, radiographic findings and spirometry with reversibility (< 15% in COPD). Data were assessed as baseline, 3months and 6 months intervals after treatment with drugs used in the study and these data were represented as mean ± standard error of the mean (SE). Pulmonary function tests were measured by a spirometer (spirolab III) as FEV1, FEF25-75%, PEF and FEV3. In addition, assessing the plasma levels of TNF-α, MDA as markers of inflammation and oxidative stress was performed. TNF-α plasma concentrations were measured by Enzyme Linked Immunosorbent Assay (ELISA) technique. MDA plasma concentration was measured and identified as the product of lipid peroxidation that react with thiobarbituric acid to give red species absorbing at 535 nm.

Results:

The data in table (1) showed that FEV1 values in patients treated with telmisartan and those treated with both telmisartan and simvastatin for 3 and 6 months were significantly higher ($p<0.05$) than that of the control group of patients. Meanwhile, patients that took simvastatin 20mg/d for 6 months also showed a significant increase ($p<0.05$) in FEV1 values as compared to that of control group of patients. There was a significant improvement in FEV1 values in patients taking telmisartan 40mg/d for 6 months as compared to the three month period of treatment by the same drug. While the decline of FEV1 values in the control group of patients after 6 months was significant ($p<0.05$), as compared to baseline values in the same group of patients. As shown in table (2), patients treated with telmisartan and those treated with combination of both telmisartan and simvastatin for 3 and 6 months showed a significant increase ($p<0.05$) in FEF25-75 values as compared to pretreatment values and values in the control group of patients at the same time period. Meanwhile, patients treated with simvastatin 20mg/d for 3 and 6 months showed a significant increase ($p<0.05$) in FEF25-75 values as compared to pretreatment values. In this group of patients, only after 6 months, there was a significant increase ($p<0.05$) in FEF25-75 values as compared to control group of patients. Baseline values of FEF25-75 in all study groups were significantly lower ($p<0.05$) from those in normal healthy individuals. The data in table (3) showed that patients treated with simvastatin 20mg/d, telmisartan 40mg/d and those treated with combination of both, showed a significant increase ($p<0.05$) in PEF values after 3 and 6 months of treatment as compared to that of control group of patients at the same time course. However, in the control group of patients, the decline in PEF continued and it was significant ($p<0.05$) at the 3 and 6 months values as compared to the pretreatment level and between 3 and 6 months time period in the same group. As shown in table (4), patients treated with simvastatin 20mg/d, telmisartan 40mg/d and those treated with combination of both, showed a significant increase ($p<0.05$) in FEV3 values after 3 and 6 months of treatment from that of control group of patients at the same time course. This means that there was a parallel improvement in FEV3 to the decline in the control group, in this parameter after 3 and 6 months period. However, in the control group of patients, the decline in FEV3 continued, and there was a significant reduction ($p<0.05$) after 3 and 6 months as compared to the pretreatment values. Baseline values and after 3 and 6 months values of FEV3 in patients of all study groups were significantly lower ($p<0.05$) than those of normal group of healthy individuals at the same time period. This means that even after significant improvement in FEV3 values after 3 and 6 months, these values were still far from that of normal healthy individuals. The data in table (5) showed that, in patients treated with simvastatin 20mg d, there was a significant reduction ($p<0.05$) in TNF- α values after 3 and 6 months of treatment as compared to those of pretreatment and control group values of patients at the same time period. The same thing was recorded for patients treated with telmisartan 40mg/d and those treated with combination of both simvastatin and telmisartan, where the values of TNF- α were significantly lower ($p<0.05$) after 3 and 6 months of treatment from that of pretreatment values and those of control group of patients at the same time period. However, these two last groups of patients also showed significant decrease ($p<0.05$) in TNF- α values after 6 months period of treatment as compared to 3 months period of treatment with the same drugs. In table (6), the data showed that the baseline values of MDA in patients treated with telmisartan and those treated with combination of simvastatin and telmisartan showed a significant increase ($p<0.05$) from that of baseline values of MDA in normal group of healthy individuals. After 3 and 6 months treatment with telmisartan or with combination of simvastatin and telmisartan, values of MDA were significantly reduced ($p<0.05$) as compared to pretreatment values. Patients treated with simvastatin 20mg/d for 6 months showed a significant decrease in MDA values

($p<0.05$) from that of pretreatment values.

Discussion:

In this study, pulmonary function tests indicates that there was a statistically significant improvement in this function after treatment courses of 3 and 6 months with simvastatin 20mg/d, telmisartan 40mg/d and the combination of both as was shown in tables (1 – 4), where FEV1, FEF25-75, PEF and FEV3 values showed statistically significant improvement after treatment with the above mentioned drugs. These results were in agreement with other results that also indicate attenuation of lung function decline in statin users and telmisartan users on COPD patients (11, 12). However, combination of the two drugs or the use of telmisartan alone as a prospective study had not yet been studied. Few studies have been published and examined the effect of statins on lung function. A recent abstract published for the Chest 2006 conference examined the effects of statin use on lung function in 485 elderly subjects who were current or former smokers. This work reported reduced declines in FVC and FEV1 for statin users compared with nonusers (11). The anti-inflammatory and immunomodulatory properties and capability of simvastatin, telmisartan and their combination were obvious in this work as shown in table (5), where the results showed that there was a marked and significant reduction in TNF-α values in patients with COPD after receiving simvastatin 20mg/d, telmisartan 40mg/d or their combination. However, combination of these two drugs showed a more powerful effect to reduce this immune and inflammatory marker than if either drug was used alone. Increasingly, more studies have shown that tumor necrosis factor-α (TNF-α) plays an important role in the pathogenesis of COPD (13) and is involved in the induction of apoptosis of endothelial cells, such as human coronary artery endothelial cells (14) and pulmonary artery endothelial cells in experimental idiopathic pneumonia syndrome (15). Effects of simvastatin 20mg/d, telmisartan 40mg/d and their combination on oxidative stress marker (MDA), was also obvious as shown in table 6 where these two drugs were able to reduce the oxidative stress marker significantly after 3 and 6 months of treatment. Other studies were in agreement with these results (16, 17). Systemic oxidative stress is also increased in patients with COPD, particularly during exacerbations, and this is linked to reduced antioxidant capacity (16). Although 3-hydroxy-3-methyl-3-glutaryl coenzyme A reductase inhibitors reduce cholesterol, they have several other pharmacological actions that might be beneficial in COPD, including antioxidant, antiinflammatory, and immunomodulatory effects (17).

Conclusion:

The anti-inflammatory, antioxidant effects of simvastatin and telmisartan were associated with improved pulmonary function and there may be a potentiation effect between statins and angiotensin receptor blockers (ARBs) that require further approval.

Table (1): Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on FEV1 in patients with mild to moderate COPD, after 3, 6 months of treatment, untreated group of COPD patients (control) and normal healthy individuals.

Groups	Number of subjects	FEV1 (L)		
		pretreatment	3months	6months
Normal	20	4.06 ± 0.07	3.99 ± 0.05	4.03 ± 0.08
Control	20	1.66 ± 0.06 *	1.57 ± 0.06 *	1.45 ± 0.06 *a
Simvastatin	20	1.71 ± 0.07 *	1.79 ± 0.1 *	1.85 ± 0.1 *b
Telmisartan	20	1.82 ± 0.06 *	1.88 ± 0.07 *b	1.97 ± 0.08 *cb
Simvastatin + Telmisartan	20	1.74± 0.09 *	1.87 ± 0.09 *b	1.94 ± 0.08 *b

Values expressed as mean ± standard error of mean.
* Significantly different ($p<0.05$) as compared with normal values.
a Significantly different ($p<0.05$) as compared with pretreatment values.
b Significantly different ($p<0.05$) as compared with control values.
c Significantly different ($p<0.05$) as compared between 3 and 6 months values.

Table (2): Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on FEF25-75% in patients with mild to moderate COPD, after 3, 6 months of treatment, untreated group of COPD patients (control) and normal healthy individuals.

Groups	Number of subjects	FEF25-75 (L/S)		
		pretreatment	3months	6months
Normal	20	4.67 ± 0.12	4.58 ± 0.11	4.64 ± 0.14
Control	20	1.97 ± 0.1 *	1.96 ± 0.06 *	1.8 ± 0.05 *
Simvastatin	20	1.79 ± 0.08 *	2.19 ± 0.1 * a	2.22 ± 0.1 *ab
Telmisartan	20	1.92 ± 0.1 *	2.3 ± 0.09 *ab	2.41 ± 0.1 *ab
Simvastatin + Telmisartan	20	1.88 ± 0.1 *	2.27 ± 0.09 *ab	2.4 ± 0.08 *ab

Values expressed as mean ± standard error of mean.
* Significantly different ($p<0.05$) as compared with normal values.
a Significantly different ($p<0.05$) as compared with pretreatment values.
b Significantly different ($p<0.05$) as compared with control values.

Table (3): Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on PEF in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals. Values expressed as mean ± standard error of mean.

Groups	Number of subjects	PEF (L/S)		
		pretreatment	3months	6months
Normal	20	4.86 ± 0.13	4.74 ± 0.11	4.83 ± 0.12
Control	20	2.5 ± 0.09 *	2.09 ± 0.08 *a	1.88 ± 0.06 *ac
Simvastatin	20	2.31 ± 0.09 *	2.48 ± 0.12 *b	2.5 ± 0.09 *b
Telmisartan	20	2.43 ± 0.11 *	2.62 ± 0.12 *b	2.66 ± 0.11 *b
Simvastatin + Telmisartan	20	2.49 ± 0.1 *	2.81 ± 0.17 *b	2.78 ± 0.13 *b

* Significantly different ($p<0.05$) as compared with normal values.
a Significantly different ($p<0.05$) as compared with pretreatment values.
b Significantly different ($p<0.05$) as compared with control values.
c Significantly different ($p<0.05$) as compared between 3 and 6 months values.

Table (4): Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on FEV3 in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Groups	Number of subjects	FEV3 (L/S)		
		pretreatment	3months	6months
Normal	20	4.77 ± 0.14	4.64 ± 0.17	4.75 ± 0.19
Control	20	2.23 ± 0.07 *	1.97 ± 0.06 *a	1.9 ± 0.06 *a
Simvastatin	20	2.19 ± 0.08 *	2.37 ± 0.11 *b	2.38 ± 0.1 *b
Telmisartan	20	2.19 ± 0.1 *	2.32 ± 0.12 *b	2.39 ± 0.11 *b
Simvastatin + Telmisartan	20	2.3 ± 0.13 *	2.46 ± 0.17 *b	2.53 ± 0.13 *b

Values expressed as mean ± standard error of mean.
* Significantly different ($p<0.05$) as compared with normal values.
a Significantly different ($p<0.05$) as compared with pretreatment values.
b Significantly different ($p<0.05$) as compared with control values.

Table (5): Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on TNF-α in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Groups	Number of subjects	TNF-α (ng/L)		
		pretreatment	3months	6months
Normal	20	2.09 ± 0.26	2.04 ± 0.3	2.03 ± 0.22
Control	20	18.6 ± 1.43 *	19.95 ± 1.84 *	20.06 ± 1.49 *
Simvastatin	20	20.13 ± 1.52 *	10.49± 1.4 *ab	4.5 ± 1.06 *abc
Telmisartan	20	16.9 ± 0.87 *	9.61 ± 1.1 *ab	4.61 ± 0.73 *abc
Simvastatin+ Telmisartan	20	17.6 ± 0.83 *	9.44 ± 1.12 *ab	2.9 ± 0.17*abce

Values expressed as mean ± standard error of mean.
* Significantly different ($p<0.05$) as compared with normal values.
a Significantly different ($p<0.05$) as compared with pretreatment values.
b Significantly different ($p<0.05$) as compared with control values.
c Significantly different ($p<0.05$) as compared between 3 and 6 months values.
e Significantly different ($p<0.05$) as compared telmisartan and the combination group of values.

Table (6): Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on MDA in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Groups	Number of subjects	MDA (mmol/L)		
		pretreatment	3months	6months
Normal	20	0.73 ± 0.06	0.71 ± 0.05	0.72 ± 0.07
Control	20	2.57 ± 0.2 *	2.65 ± 0.23 *	2.75 ± 0.21 *
Simvastatin	20	3.16 ± 0.22 *	2.98 ± 0.25 *	2.43 ± 0.17 *a
Telmisartan	20	3.1 ± 0.14 *b	2.63 ± 0.16 *a	2.18 ± 0.15 *ab
Simvastatin + Telmisartan	20	3.41 ± 0.17 *b	2.52 ± 0.24 *a	1.99 ± 0.17 *ab

Values expressed as mean ± standard error of mean.
* Significantly different ($p<0.05$) as compared with normal values.
a Significantly different ($p<0.05$) as compared with pretreatment values.
b Significantly different ($p<0.05$) as compared with control values.

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