ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 27-08-2013
Accepted: 29-09-2013

Vol. 2 No. 10 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

The Modern Aspects of Immune Corrective Therapy in Patients with Chronic Obstructive Pulmonary Disease with Metabolic Syndrome

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Chronic obstructive pulmonary disease (COPD), along with hypertension, ischemic heart disease and diabetes is a leading a group of chronic diseases, which account for over 30% of all other human pathology. The leading cause of mortality in patients with light and medium heavy flow COPD is not respiratory failure, as traditionally believed, but cardiovascular disease - hypertension, coronary heart disease, which are components of the metabolic syndrome (Met S). The purpose of study was to identify clinical and immunological effectiveness of atorvastatin and polyoxidonium in patients with COPD, combined with Met S. The study involved 75 patients with COPD stage II and Met S. Some immunological tests of I and II levels were performed before and after treatment by statins. The combined use of atorvastatin and polyoxidonium shows significant clinical and immunological efficacy, which is to restore the values of healthy individuals phagocytic activity of neutrophils, reducing autoimmune manifestations, phenomena of auto sensibilization and has powerful anti-inflammatory properties.

Keyword: Chronic Obstructive Pulmonary Disease, Metabolic Syndrome, Immunity, Treatment

1. Introduction

In the modern world chronic obstructive pulmonary disease (COPD), along with hypertension, ischemic heart disease and diabetes is a leading a group of chronic diseases, which account for over 30% of all other human pathology. WHO classifies COPD to diseases with high social encumbrances[1, 2, 3] and according to expert forecasts, by 2020 COPD will reach the third place among all causes of death. Unfavorable prognosis of COPD is associated with a particular variant of inflammation that responds poorly to the control and has features of a systematic process.

The leading cause of mortality in patients with light and medium heavy flow COPD is not respiratory failure, as traditionally believed, but cardiovascular disease - hypertension, coronary heart disease, which are components of the metabolic syndrome (MS)[1].

In current clinical practice is increasingly found the patients with all three diseases - diabetes, hypertension, coupled with coronary artery disease and COPD. The set of socially significant diseases reflects the new phase of disease of the century. Thus, MS, on the one hand, and the violation of bronchial obstruction and reduced lung function, on the other hand, may mutually potentiate each other[1].

According to the literature it is known that there is an increase of inflammatory markers in the blood in patients with COPD even during clinical remission[4]. The combination of MS with COPD leads to the fact that the level of inflammatory

markers is extremely high, it is difficult controlled by bronchodilators and statins, clinically manifested as frequent exacerbations of COPD with the development of remodeling of the bronchial tree and symptoms of complications of the cardiovascular system and destabilization of atherosclerotic plaques[5, 6].

The purpose of study was to identify clinical and immunological effectiveness of atorvastatin and polyoxidonium in patients with COPD, combined with MS.

2. Materials and methods

The study involved 75 patients with COPD stage II and MS, whose average age was 51.3+4.2 years. The diagnosis of COPD is established according to the Order of Ministry of Health of Ukraine No. 128[7]. The diagnosis of MS is established on the basis of detailed anamnesis, clinical, laboratory and instrumental methods in identifying the main criteria for the syndrome on the recommendations of the International diabetes Federation (IDF), 2005[8]. All patients were examined in remission of COPD and were treated by basic therapy with prolonged inhaled anticholinergic drugs (tiotropiy bromide 18 mg per day) and short-acting drugs on demand without inhaled corticosteroids.

In order to correct existing violations of lipid metabolism in MS received atorvastatin at a daily dose of 10 mg. To achieve the target blood pressure levels, all patients received enalapril at a daily dose of 20 - 40 mg, with little effect was added amlodipine at 10 mg. Polyoxidonium administered intramuscularly at a dose of 6 mg a day (10 injections) against the continuation of statin therapy.

The control group consisted of 35 healthy people randomized by age and sex, with no signs of MS and COPD. All patients were evaluated to indicators of immune status, which included the tests I and II levels as required by the Memorandum of WHO[9] quantify the major populations and subpopulations of lymphocytes , determination of activated subpopulations of lymphocytes CD54+, CD95+, HLA -DR+, CD25+, levels of pro-and anti-inflammatory cytokines to determine spontaneous and mitogen-induced lymphocyte proliferative activity, the level of circulating immune complexes (CIC) of different molecular weight in the serum and the phagocyte activity of peripheral blood neutrophils , the concentration of serum immunoglobulin (IgG, IgA, IgM). Immunological examination was performed three times: before carrying statin therapy than in dynamics in 3 months of continuous use of atorvastatin and even after 1 month of combined treatment with additional inclusion of polyoxidonium.

3. Results and Discussion.

As a result of the research found that the total number of leukocytes, the relative content of CD3+ and CD16+ cells in peripheral blood had no significant differences from values in healthy individuals in the dynamics as during treatment with statins and combination of statins with polyoxidonium ($p>0,05$).

However, if on the background of using only the atorvastatin the relative number of peripheral blood lymphocytes decreased from the initial value to 11, 51% ($p<0,05$), then the background of combined treatment with polyoxidonium - by 21, 82% ($p<0,05$) to the values of the control group (Table 1). Also found a positive effect on the level of CD22+ cells - the dynamics of statin treatment was observed decrease in the percentage of CD22+ cells at 12,37% ($p<0,05$), and the combination of atorvastatin and polyoxidonium led to a further reduction of these cells by 42,11 % ($p<0,05$) to the level of healthy individuals ($p>0,1$).

Considerable attention was paid to the data of the effectiveness of statin therapy in restoring polyoxidonium quantification of major immunoregulatory subpopulations: in dynamics with the inclusion of atorvastatin treatment was a significant decrease in immunoregulatory index in 1.17 times, and combination therapy with polyoxidonium - further its normalization at 38,43% ($p<0,05$).

The use of combined therapy helped to reduce the number of activated lymphocyte subpopulations: the content of CD25+ lymphocytes in the dynamics of atorvastatin treatment significantly decreased by 24,8% ($p<0,05$), but by adding

polyoxidonium - in general the 72,49% (p<0,05) to the values of the control group. Similar to standard values decreased the content of CD95+ lymphocytes after adding the polyoxidonium.

Table 1: The relative content of basic and activated populations and subpopulations of lymphocytes in patients with COPD, combined with MS, in the combined treatment with the inclusion of polyoxidonium (M±m)

Index	Before treatment (n=75)	After treatment (n=75)		Control group (n=35)
		After 3 months	After 4 months	
Leucocytes, 10^9/л	6,36±1,19	6,25±1,09	6,92±0,98	6,76±0,82
Lymphocytes, %	41,15±2,75 *	36,42±2,18* x	32,17±2,11 **	31,64±3,90
$CD3^+$ lymphocytes, %	61,30±2,86	64,55±3,68	66,82±3,54	65,85±6,55
$CD4^+$ lymphocytes, %	41,78±1,86*	37,62±1,26* x	34,11±1,19 **	33,23±3,90
$CD8^+$ lymphocytes, %	17,24±0,85*	18,28±0,95 *	23,06±0,71 **	21,50±2,01
$CD4^+/CD8^+$	2,42±0,13*	2,07±0,11* x	1,49±0,08**	1,55±0,29
$CD22^+$ lymphocytes,%	31,45±1,13*	27,56±1,12*x	22,13±1,05**	24,03±1,50
$CD16^+$ lymphocytes,%	16,92±0,93	17,34±1,02	18,93±1,04	18,85±2,30
$CD25^+$ lymphocytes,%	15,61±0,45*	11,74±0,36* x	9,05±0,31**	8,96±0,39
HLA-DR^+ lymphocytes,%	17,61±0,29*	15,47±0,21* x	15,24±0,48 *	12,3±1,27
$CD95^+$ lymphocytes,%	7,35±0,11*	5,16±0,08* x	3,14±0,07**	3,04±0,09
$CD54^+$ lymphocytes,%	21,02±1,01*	17,73±0,89* x	16,82±0,96*	11,07±1,65

Notes:
* - probability of difference of the control (p <0.05);
X-likelihood difference in the dynamics of statin treatment (p <0.05);
** - Likely difference in the dynamics of statin treatment and PO (p <0.05);
N-number of patients

If the relative number of activated lymphocytes expressing the early activation marker (α- chain of IL-2 receptor) and FAS- receptor reached the level of healthy individuals, the content of activated T and B cells from the late activation marker levels remained higher than the control group at 23,9%, indicating that the combined use of atorvastatin and polyoxidonium effectively reduces the number of circulating auto antigens (level of low-density lipoprotein, auto antigens damaged vessel wall) that cause uncontrolled activation of immune cells, but has an excess of activated cells remain and can be eliminated only after a certain period of time. Similar changes were found in the quantitative composition of CD54+ lymphocytes, their levels higher than rate in healthy subjects at 52.82%, which indicates an increase in the ability of lymphocytes and other cells to the peripheral blood adhesion is important pathogeneses chain increased clotting as in MS or COPD of severe stages.

As can be seen from the data presented in Table 2, the combined co-administration of statins and polyoxidonium contributed significant decrease in spontaneous proliferative activity of lymphocytes in 1.74 times (p<0,05) to values in healthy subjects , although a positive trend was observed already during treatment statins

(p<0,05). Also, the dynamics of treatment was observed and reduced PHA -stimulated lymphocyte proliferative activity during treatment with atorvastatin alone , which may be due to both the anti-inflammatory effects of statins and the decrease in the activity of microbial and viral antigens as factors causing exacerbation of COPD (for the period observations in patients with no exacerbations of COPD). However, the most effective was the combination of atorvastatin and polyoxidonium on the phagocyte parts of the immune system. We found the growth of phagocytes parameter number to 37,61% (p<0,05), phagocyte index - by 27,16% (p<0,05), both indicators have reached the normative values (p>0,1). It should be noted that treatment with atorvastatin also had a positive, albeit insufficient, impact on the performance of the phagocyte component of the immune system, and that the effects of polyoxidonium to restore these parameters led to these changes.

Table 2: Dynamics of indicators of functional activity of immunocompetent cells in COPD patients with MS in the combined treatment with atorvastatin and polyoxidonium (M±m)

Index	Before treatment (n=75)	After treatment (n=75)		Control group (n=35)
		After 3 months	After 4 months	
RBTL spontaneous%	3,18±0,11*	2,74±0,09*x	1,83±0,12**	1,76±0,61
RBTL with PHA,%	89,41±3,22*	79,45±3,06x	78,56±2,68	80,0±4,70
Phagocytic number	4,68±0,17*	5,31±0,21*x	6,44±0,27**	6,50±0,60
Phagocytic index,%	51,26±2,52*	60,21±2,43x	65,18±2,31**	69,80±7,20

Notes:
* - probability of difference of the control (p <0.05);
X-probability of difference of the dynamics of statin treatment (p <0.05);
** - probability of difference of the dynamics of statin treatment and PO (p <0.05);
N-number of patients

Investigation of serum immunoglobulin in the dynamics of treatment showed that the content of IgG had no significant differences (p>0,05) and remained higher than in healthy individuals (p<0,05); IgA levels were lower than in the control group at 30, 26% (p<0,05), on the background of atorvastatin treatment had no significant changes (p>0,05), and by adding polyoxidonium significantly increased by 18,87% (p<0,05), but has not reached the standard values. Content serum IgM had no significant differences from those in healthy individuals in the dynamics of treatment.

Particularly noteworthy are the data on the recovery ratio of CIC in the serum of patients with COPD with MS in the combined use of atorvastatin and polyoxidonium. Initial positive effect on the concentration of CIC was marked by the application of atorvastatin: the level of pathogenic CIC small and medium size decreased respectively 1,31 (p<0,05) and 2.15 times (p<0,05), but both values significantly exceeded the levels in healthy subjects in 1,36 (p<0,05) and 2.23 times (p<0,05), and the level of physiological CIC large in dynamic treatment increased in 1.59 times (p<0,05, but has not reached the performance of the control group and remained lower at 1.53 times (p<0,05). In addition to atorvastatin appointment of polyoxidonium helped to reduce serum concentrations of pathogenic CIC of small and medium size (p<0,05) and increased the content of CIC large sized (p<0,05) to the level of healthy individuals (p>0,05), which is caused by the reduction of phagocytic activity of neutrophils and elimination of CIC as well as reduction of

phenomena of auto sensibilization and auto activation of immune system (Table 3).

Table 3: Dynamics of humeral immunity of patients with COPD with MS in the combined treatment with atorvastatin and polyoxidonium (M±m)

Index	Before treatment (n=75)	After treatment (n=75)		Control group (n=35)
		After 3 months	After 4 months	
Ig G, g/l	16,28±1,17*	16,36±1,05*	15,95±1,11*	12,68±1,42
Ig A, g/l	1,06 ±0,13*	1,02±0,08*	1,26±0,07**	1,52±0,19
Ig M, g/l	0,95±0,10	0,97±0,11	0,96±0,08	0,98±0,09
CIC large sized (> 19S), conventional units	21,17±0,49*	33,75±1,12* x	48,76±1,84**	51,7±3,12
CIC medium size (11-19S), conventional units	61,55±2,34*	46,94±1,63 * x	36,11±1,75**	34,54±2,02
CIC of small size (<11 S), conventional units	52,37±1,72*	24,39±1,05 * x	11,41±1,12**	10,94±1,13

Notes:
* - probable difference in the control group (p <0.05);
X-likelihood difference in the dynamics of statin treatment (p <0.05);
** - Likely difference in the dynamics of statin treatment and PO (p <0.05);
N-number of patients

From the data that are presented in Table. 4 seen that the dynamics of atorvastatin treatment in patients with COPD with MS decreased serum concentrations of TNF-α at 1.64 times (p<0, 05), IL-1β - at 1.46 times (p<0, 05) and IL-6 - at 2.77 times (p<0, 05) from baseline. However, their content is significantly lower than in healthy individuals.

Table 4: Serum concentrations of cytokines in patients with COPD with MS in the combined treatment with atorvastatin and polyoxidonium (M±m)

Index	Before treatment (n=75)	After treatment (n=75)		Control group (n=35)
		After 3 months	After 4 months	
TNF-α, pg / ml	126,9±7,5*	77,9±3,12*x	45,58±2,64 **	42,3±4,9
IL-1β, pg / ml	105,1±6,8*	72,6±3,82 * x	44,85±3,17**	39,42±4,5
IL-6, pg / ml	68,3±2,2*	24,71±1,31 * x	15,26±1,05* **	10,31±2,3
IL-4 pg / ml	17,5±1,1*	22,72±1,2 x	24,08±1,31**	25,42±3,3

Notes:
* - probable difference in the control group (p <0.05);
X-likelihood difference in the dynamics of statin treatment (p <0.05);
** - Likely difference in the dynamics of statin treatment and PO (p <0.05);
N-number of patients

It was also found reducing anti-inflammatory IL-4, which is against the background of a 3-month treatment with atorvastatin significantly increased to 1.3 times the level of healthy individuals (p>0, 1). Adding to atorvastatin the immune tropic Polyoxidonium contributed more complete recovery indicators of cytokine status with significant reduction in pro-inflammatory cytokines.

4. Conclusions

1. It is established that statin therapy (atorvastatin) has the immune corrective properties in patients with COPD and MS that experienced a reduced level of auto sensibilizatory events and anti-inflammatory properties.
2. The combined use of atorvastatin and polyoxidonium shows significant clinical and immunological efficacy, which is to restore the values of healthy individuals phagocytic activity of neutrophils, reducing autoimmune manifestations, phenomena of autosensibilization and has powerful anti-inflammatory properties.
3. Patients with COPD combined with MS during the remission of COPD in addition to statin therapy is the appropriate appointment of polyoxidonium at a dose of 6 mg intramuscularly every other day in a course of 10 injections.

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