Presently, utilization of compound preparations including inhaled glucocorticosteroids and prolonged $\beta_2$-agonists are recommended by national and international consensuses to gain control in moderate and severe poorly controlled bronchial asthma (BA) as first line therapy \cite{5, 10, 12, 19, 20}.

However, exists a category of patients, in whom clinical, functional and laboratory symptoms of asthma persist, despite of anti-inflammatory therapy using combined medicines \cite{3, 10, 11, 12, 15, 19}.

In patients with severe bronchial asthma life quality deteriorates significantly, with high risk of invalidization and treatment, associated with considerable economic costs \cite{3, 5, 9, 11, 18, 21}.

The characteristic symptoms of severe BA are: permanent occurrence of daily symptoms, frequent exacerbations, frequent night symptoms, restrictions of physical activity, FEV$_1$ (forced expiratory volume) or PEFR (peak expiratory flow rate) < 60\% of predicted or personally best, PEFR or FEV$_1$ diurnal variability > 30\%, increase of frequency of using of short acting $\beta_2$-agonists (over 8 inhalations within one day), oral GCS administration courses (over 2-3 times a year), as well as frequent emergency ambulance calls \cite{11, 15}.

In functional terms, the symptom of severe BA is absence of complete reversibility and fixed bronchial obstruction of various degree of manifestation, accelerated decrease of FEV$_1$, increase of spontaneous or induced bronchial hyperreactivity, FEV$_1$ daily variability, reduction of response to $\beta_2$-agonists \cite{9, 13, 14, 16, 17, 22}.

Besides, reduction of lungs elastic response is observed in these patients, which is shown as bronchial tubes collapse and leads to increase of airways resistance of development pulmonary hyperinflation, exasperation of short-breathing and reduction of physical exercise tolerance \cite{15, 16, 17, 18, 22}.

This occurs due to the fact that organic changes in the bronchial wall are developed in patients with severe BA, bronchial obstruction is added, and the influence of parasympathetic nervous system becomes stronger \cite{14, 15, 21, 22}.

Contents of both eosinophils and neutrophils are increased in the induced sputum in this group of patients, that is, pathophysiological changes which to a greater extent characteristic of chronic obstructive pulmonary disease (COPD) \cite{1, 9, 13, 14, 17, 18}.

In this connection, addition of therapeutic regimens used at COPD, in particular, planned therapy with anticholinergic drugs, to baseline therapy may be pathogenically relevant \cite{15, 16, 17, 18, 22}.

Anticholinergic drugs block muscarinic receptors of tracheobronchial tree prevent and inhibit endogenous bronchial obstruction stimulated by increased n. Vagus tone, block refractory bronchial spasm related to effect of smoking, industrial and household triggers, reduce secretion of bronchi mucous membrane, reduce pulmonary hyperinflation \cite{4, 7, 8, 11, 20}.

Efficiency of using of tiotropium bromide in COPD treatment, based on the evidence-based medicine, a certain similarity of pathophysiologic mechanisms and clinical and functional disorders at COPD and severe BA allowed us to use this medicine in combined complex baseline therapy of patients with severe BA.

Aim of the study: to investigate clinical and functional efficiency of complex therapy of severe persisting BA patients using a compound medicine (salmeterol / fluticasone propionate) in combination with tiotropium bromide.

Materials of the study:
30 patients aged 37-75 took part in the study, 12 male and 18 female with stable severe BA, FEV₁ < 60% of pred., with positive test of bronchial reversibility. The patients received outpatient treatment in the State institution “Institute of phthisiology and pulmonology at the NAMS of Ukraine”.

The 1st group consisted of 7 male and 8 female, their average age (56.3 ± 2.6) years old; average disease duration = (15.9 ± 1.4) year; smoking history (13.7 ± 1.9) “pack/years”, the majority quitted smoking immediately after beginning of the disease; FEV₁ (43.6 ± 2.8) % of pred.

The 2nd group consisted of 6 male and 9 female, their average age (55.7 ± 2.4) years old; average disease duration = (15.6 ± 1.5) year; smoking history (12.8 ± 1.8) “pack/years”; FEV₁ mean value made (48.1 ± 2.8) % of pred.

Upon “washing-out” period during two weeks (fluticasone propionate 125 μg - 2 inhalations (250 μg) 2 twice a day, short actins β₂-agonists - salbutamol –PRN) the patients were randomized 1:1 for further course of treatment during 2 months.

The patients of the 1st group received during 2 months: salmeterol/fluticasone propionate 50/250 μg and tiotropium bromide (18 μg capsules with powder for inhalations) – one capsule per day.

The patients of the 2nd group received only - salmeterol/fluticasone propionate 50/250 μg - 1 inhalation twice per day.

The results were under examination: dynamics clinical symptoms (asthma score, use of β₂-agonists PRN according to self-observation journal); respiratory function indices spirometry with analysis the forced expiration "flow-volume" curve and whole-body plethysmography (on the "MasterLab" apparat, "Erich Jaeger"), respiratory muscles strength ("MasterScope", "Erich Jaeger"); Peak flow meter ("Vitest").

Results: according to analysis of the self-observation journals, the number of night symptoms reduced reliably (p < 0.01) in patients of the 1st group vs to the baseline data — from (1.99 ± 0.06) to (0.82 ± 0.06); morning chest tightness — from (1.63 ± 0.07) to (0.73 ± 0.05); the number of daily symptoms — from (2.35 ± 0.06) to (1.19 ± 0.06); cough — from (1.86 ± 0.05) to (1.01 ± 0.08); dyspnoe score — from (3.3 ± 0.3) to (1.5 ± 0.3). Need rescue medication reduced reliably (p < 0.01) from (3.9 ± 0.6) in the beginning to (1.5 ± 0.2) times after the course of treatment (figure 1).

In the 2nd group of patients, the following were reliably (p < 0.01) reduced in the course of treatment: night symptoms — from (1.91 ± 0.13) to (1.46 ± 0.11); daily symptoms — from (1.91 ± 0.11) to (1.39 ± 0.10); dyspnoe score — from (1.8 ± 0.2) to (1.2 ± 0.2). Other indicators — morning chest tightness, cough during the day, as well as the number of β₂-agonists inhalations only had a tendency to reduction. The dynamics of clinical symptoms in patients of the 2nd group based on the data of self-observation journals is represented on figure 2.

Analysis of the obtained data demonstrated that reliable (p < 0.05) inspiratory capacity increase was observed in patients of the 1st group as compared with patients of the 2nd group (by 44.2 %), as well as more expressed but not reliable reduction of the residual volume and functional residual lung capacity.

A positive dynamics among the bronchial permeability indicators was also observed in patients of the 1st group. Thus, by the end of the 1st month of treatment, FEV₁ reliably (p < 0.05) increased vs baseline: from (42.4 ± 4.1) % to (52.1 ± 3.7) % and even to a greater extent upon termination of the treatment course — to (59.3 ± 4.8) %. The following factors increased statistically reliable (p < 0.05) as compared baseline data: FEF₅₀ from (22.2 ± 3.2) % to (33.7 ± 4.0) % upon the 1st month of treatment and to (37.5 ± 5.4) % upon termination of the treatment course, FEF₂₅ — from (21.5 ± 2.0) % to (33.2 ± 3.8) % (p < 0.05) upon the 1st month and to (36.2 ± 4.1) % (p < 0.05) upon the end of the study, bronchial permeability on the level of 75-85 % of the forced vital lung capacity by the end of the first month of treatment increased by 60 %, and upon ter-

Figure 1 Dynamics of BA clinical symptoms in patients of the 1st group.

* p < 0.01 as compared to the baseline data.
mination of the treatment course under consideration — virtually twice (figure 3).

FEV1/FVC also changed (p < 0.05) in two months of treatment from (59.0 ± 1.1) to (77.2 ± 1.4) %.

Statistically valueless dynamics of main respirometry indicators was observed in patients of the 2nd group. Thus, forced expiratory volume for the first second, indicators of permeability on the level of medium bronchi and bronchial tubes increased slightly.

The data obtained testify to the fact that addition of tiotropium bromide to the complex anti-inflammatory therapy salmeterol/fluticasone propionate combination in severe persisting BA patients during 2 months of was more efficient regimen, compared to the salmeterol/fluticasone propionate combination:

1. More expressed and earlier reduction of asthma symptoms, need of rescue medication.
2. Significant improvement of bronchial permeability - reliable increase of FEV1, FEV1/FVC, FEF25, FEF75.
3. Reduction of pulmonary hyperinflation, which was confirmed by a reliable increase of inspiratory capacity, reduction of functional residual lung capacity and residual volume.
Thus, addition of tiotropium bromide to the combination of ICS and β2-agonists of prolonged action is pathogenically justified, allows significantly reduce symptoms, need of rescue medication, improving respiratory function and optimizing control over the disease in severe BA patients.

References