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Assessment of the acute bronchodilator test and the efficacy of the course of treatment with Glycopyrronium bromide in patients with pulmonary tuberculosis associated with chronic obstructive pulmonary disease

M.F. Yaushev[1]*, A.P. Alexeev[2]

[1]Kazan State Medical University, Kazan, Russia;
[2]Republic Clinical Anti-Tuberculosis Dispensary, Kazan, Russia

Abstract

Background. Despite significant progress in the fight against tuberculosis, the number of new cases in the world remains relatively stable, and amounts are more than 10 million annually. Chronic obstructive pulmonary disease (COPD) negatively affects the quality of life in patients with pulmonary tuberculosis and reduces the effectiveness of chemotherapy. Correction of bronchial obstruction in pulmonary tuberculosis remains an actual problem.

Aim. To assess the acute bronchodilator test with glycopyrronium bromide, pulmonary function test parameters changing within 24 hours after inhalation, as well as the effect of a 2–3-month course of treatment with glycopyrronium bromide on the same parameters and the quality of life in patients with pulmonary tuberculosis associated with chronic obstructive pulmonary disease.

Material and methods. A prospective cohort study of 38 patients with active pulmonary tuberculosis associated with the chronic obstructive pulmonary disease treated with anti-tuberculosis chemotherapy was carried out. The pulmonary function test parameters were assessed before inhalation, 15, 30, 120 min, 23 h 45 min after a single inhalation of glycopyrronium bromide, as well as after 1, 2 and 3 months of treatment. Quality of life was assessed by using CAT (COPD Assessment Test), SF-36 (Short Form-36 Health Survey Questionnaire), SGRQ (St. Georges Respiratory questionnaire).

Results. A single inhalation of 50 μg glycopyrronium bromide led to a significant increase in forced expiratory volume in 1 second by +15.2%, +18.3%, +22.8% and +11.2% after 15, 30, 120 minutes and 23 h 45 min, respectively. The change in forced expiratory volume in 1 second after 1, 2 and 3 months of treatment was +13.1%, +9.3% and +11.7%, respectively. The overall CAT score after 3 months decreased by 7. The mental health index SF-36 increased by 9.2 points. A decrease in SGRQ parameters was revealed: symptoms — by 21.7 points, physical activity — by 14.8 points, impact — by 18.2 points.

Conclusion. Inhaled glycopyrronium bromide 50 μg once daily can be recommended for the treatment of patients with active pulmonary tuberculosis associated with chronic obstructive pulmonary disease.

Keywords: tuberculosis, COPD, glycopyrronium bromide, FEV1, SF-36, SGRQ.

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Background

Despite significant progress in tuberculosis (TB) control in recent decades, the number of new TB cases worldwide remains relatively stable, with more than 10 million annually [1]. Along with the problem of multidrug-resistant TB and TB in patients with HIV infection, TB comorbidity has received increasing attention [2, 3].

Broncho-obstructive syndrome (BOS) in pulmonary TB (PTB), depending on the clinical form, is diagnosed with a rate of 52.7%–88.2% [4, 5]. BOS associated with TB is caused by both PTB itself and chronic obstructive pulmonary disease (COPD) [5]. Published data indicate that COPD deteriorates the quality of life of patients with PTB and reduces the efficiency of chemotherapy [6, 7]. BOS correction in PTB remains an urgent task.

Bronchodilator therapy in patients with PTB associated BOS results in clinical improvement, namely, decreased severity of dyspnea, increased

*For correspondence:umukgmu@rambler.ru

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exercise tolerance, improved external respiration, and improved quality of life of the patients [4]. Data have been published on the positive effect of long-term therapy with bronchodilators on the efficiency of anti-TB chemotherapy [8, 9]. Previously, bronchodilator therapy regimens were proposed for PTB with BOS [10].

Over the past decade, many new drugs have appeared in the arsenal of bronchodilator therapy [11]. Glycopyrronium bromide (GB) is used in the basic therapy for patients with COPD; it belongs to a group of long-acting anticholinergics with the preservation of the effect for 24 h after a single inhalation [12].

According to the National Clinical Guidelines of the Russian Respiratory Society, long-acting anticholinergics can be used in the treatment of COPD as both monotherapy and fixed combination with inhaled glucocorticoids and/or long-acting β-agonists. Long-acting anticholinergics are preferred because of their more pronounced effect on the risk of exacerbations [13].

Aim

This study aimed to evaluate the results of an acute test with GB (single inhalation of 50 μg of Seebri Breezhaler), dynamics of external respiration within 24 h after inhalation, effects of 2-month GB inhalation (50 μg once a day) on the parameters of external respiration, and the quality of life of patients with PTB associated with COPD.

Materials and methods of research

This prospective cohort study included 38 patients with PTB associated with COPD, who were at the inpatient stage of treatment at the Republican Clinical Antituberculosis Dispensary of the Ministry of Health of the Republic of Tatarstan in 2017–2020.

The inclusion criteria were as follows:

– Confirmed diagnosis of PTB

– COPD according to the respiratory function (RF) [forced expiratory volume per 1 second (FEV_1)/forced vital capacity (FVC) < 70%] after an acute test with a bronchodilator in combination with chronic smoking history

– Satisfactory general condition

– Agreement with the need for long-term use of a bronchodilator

– Ability to perform correctly the respiratory maneuvers during the study of the RF

The exclusion criteria were as follows:

– Bronchial asthma

– Serious condition

– Hemoptysis and/or pulmonary hemorrhage

– Acute phase of myocardial infarction

– Chronic heart failure

– Dyspnea at rest

– History of thoracic surgeries

– Exudative tuberculous pleurisy

– Severe side effects of GB

– Refusal of GB administration

– Extrapulmonary TB

Patients provided informed consent for the necessary examination and treatment. The study was approved by the local ethical committee of the Central Research Institute of Tuberculosis (Protocol No. 4/2 dated December 30, 2019).

The examination plan, in addition to the clinical, radiological (including high-resolution computed tomography), microbiological, laboratory, and instrumental examinations recommended in accordance with the standard for examination of patients with PTB, included an acute test with GB (once 50 μg as powder inhalation), assessment of RF before inhalation, and 15, 30, 120 min, and 23 h 45 min (next day) after GB inhalation. RF evaluation included spirometry, forced expiratory flow-volume loops, body plethysmography, and evaluation of the diffusion capacity of the lungs using the single-breath method (Medical Graphics Elite, USA).

The study of RF 23 h after GB inhalation was repeated in dynamics 30, 60, and 90 days after the start of GB treatment. The intake of bronchodilators by the patients was facilitated by the nursing staff, including weekly control over the issuance of capsules for inhalation. The clinical examination included the initial and monthly completion of the questionnaire for the COPD assessment test (CAT), assessment of the severity of dyspnea (Modified Medical Research Council Dyspnea Scale [mMRC]), survey using the short form of the questionnaire for quality of life (Short Form-36 Health Survey Questionnaire [SF-36]), and St. George's Hospital questionnaire (St. George's Respiratory Questionnaire [SGRQ]).

Statistical analysis was performed using the Statistica 6.0 package with the calculation of mean values and standard deviation (SD), using analysis of variance and correlation analysis, and paired Student's test at a significance level of $p < 0.05$.

Overall, the average patient age was 51.3 ± 11.6 years; men predominated (92.1%, n = 35), which is typical for patients with COPD. More often, a new case of PTB was diagnosed (47.4%, n = 18). Relapse of PTB (26.3%, n = 10) and chronic PTB (23.7%, n = 9) were detected less often, but equally. Thus, COPD was approximately equally diagnosed in patients with newly detected PTB and relapsed or chronic cases of PTB.

Patients with active PTB (groups IA and IB) prevailed in the dispensary registration, in 50.0%

(n = 19) and 23.7% (n = 9) of the cases, respectively. Nine patients had chronic PTB (group IIA; 23.7%). In one patient, inactive PTB was diagnosed as metatuberculous pneumosclerosis.

Among the patients who were newly diagnosed and in the whole group, infiltrative PTB was predominant (60.5%, n = 23). Fibrocavernous PTB was diagnosed less frequently (26.3%, n = 10), which together with cavernous PTB (2.63%, n = 1) accounted for 1/3 of all patients. Other clinical forms of PTB were less common and included disseminated PTB (5.3%, n = 2) and caseous pneumonia (2.63%, n = 1). Patients with destructive PTB accounted for 68.4% (n = 26). Bacterial excretion (by all methods) was detected in 27 (71.1%) patients. Multidrug-resistant TB was revealed in 10 (52.6%) patients and extensive drug-resistant TB in 2 (5.3%) patients. A high erythrocyte sedimentation rate (34.2 ± 19.5 mm/h) indicated initially severe intoxication.

Results

Based on the results of spirometry, including an acute test with GB, CAT, and assessment of the severity of dyspnea on the mMRC scale, the patients were stratified according to the severity of COPD.

Following the spirometric classification, patients with moderate COPD (68.4%) dominated the group, whereas severe (15.8%) and very severe (2.6%) COPD was less common.

According to the COPD classification, there were more patients with types A (26.3%, n = 10) and B (52.6%, n = 20) with a low frequency of exacerbations than those with types C (7.9%, n = 3) and D (13.2%, n = 5) with a high rate of exacerbations and poor prognosis. Patients were rarely hospitalized for severe exacerbation of COPD during the last year.

The average CAT score was >10 (13.3 ± 7.6) points. Majority of the patients had minor (36.8%, n = 14) and moderate (44.7%, n = 17) adverse effects of COPD. Strong (21–30 points) and very strong (>0 points) negative effects of COPD were registered in 6 (15.8%) and 1 (2.63%) patient, respectively.

The severity of respiratory failure was assessed using the mMRC scale. In most patients, dyspnea was mild (60.5%, n = 24, MRC1) or moderate (21.1%, n = 8, MRC2), whereas 5.3% (n = 2) and 10.5% (n = 4) of the patients had severe (MRC3) and extremely severe (MRC4) dyspnea. Dyspnea occurred only with significant physical exertion in 1 (2.6%) patient (MRC0).

The vast majority of patients were heavy smokers. The average smoker index was 30.9 ± 17.5, which indicates a high risk of not only COPD but also oncological diseases.

Table 1. Parameters of spirometry, body plethysmography, and diffusion capacity of the lungs of patients with pulmonary tuberculosis associated with chronic obstructive pulmonary disease at the time of inclusion in the study

Parameter	n (*n* = 38), M ± SD	% d.v. (*n* = 38) M ± SD
FVC, L	3.1 ± 0.68	71.2 ± 15.86
FEV_1, L	1.79 ± 0.49	52.3 ± 13.84
FEV_1 (after bronchodilator), L	2.08 ± 0.52	61.02 ± 14.71
FEV_1/ FVC,%	57.2 ± 10.59	—
FEV_1/ FVC (after bronchodilator),%	58.7 ± 12.78	—
PFR, l/s	4.0 ± 1.14	46.1 ± 13.95
MFR_{25}, l/s	2.3 ± 1.0	35.8 ± 14.8
MFR_{50}, l/s	1.16 ± .57	27.1 ± 11.84
MFR_{75}, l/s	0.5 ± .27	35.1 ± 18.10
Raw tot, kPa/l/s	0.25 ± 0.15	176.0 ± 110.7
TLC, L	6.29 ± 1.08	100.0 ± 16.06
RLV, L	2.71 ± 0.88	142.5 ± 44.93
RLV/TLC,%	41.99 ± 12.38	141.86 ± 36.46
DLCO (SB), mM/ min/kPa	4.95 ± 2.05	52.3 ± 19.16
DLCO/Va, mM/ min/kPa/L	1.01 ± 0.33	67.64 ± 20.60

Note: d.v., due value; FVC, forced vital capacity of the lungs; FEV_1, forced expiratory volume per 1 second; PFR, peak flow rate; MFR_{25}, MFR_{50}, and MFR_{75}, maximum flow rates at the level of FVC 25, 50, and 75%, respectively; Raw tot, total airway resistance; TLC, total lung capacity; RLV, residual lung volume; DLCO, diffusion lung capacity for CO; DLCO/Va, specific DLCO.

A study of RF was performed, including spirometry and body plethysmography, and the diffusion capacity of the lungs was evaluated using the single exhalation method before inclusion in the study (Table 1) as well as over time.

In general, moderate obstructive disorders were detected in the group, and the FEV_1/FVC ratio (%) before and after an acute test with a bronchodilator was significantly below 70%, which is a necessary condition for making a diagnosis of COPD. Along with this, an increase in the total airway resistance compared with the norm (120% d. v.) was noted.

The average total lung capacity was within the conventional norm. The normal total lung capacity associated with a high RLV as a manifestation of the “trapped air” and an increase in the ratio of the RLV to the total lung capacity supports the predominance of the mixed obstructive–restrictive type of ventilation disorders in the patients. Restrictive disorders are caused by the presence of chronic and/or generalized PTB in approximately 1/3 of the patients. These RF disorders should be considered specific for PTB associated with COPD.

The low initial value of the diffusion capacity of the lungs for CO (52.3 ± 19.16% d.v.) in the total group in combination with a low value of the specific diffusive capacity of the lungs for CO (67.64 ±

20.60% d.v.) indicated the presence of true diffusion disorders. This may be associated with both the presence of pulmonary emphysema and infiltrative and/or fibrous changes in the lung tissue due to PTB.

With high-resolution computed tomography, emphysema was detected in 65.8% of the patients, with emphysematous bullae having a diffuse location (in all lobes) in 43.7%. Multifocal location (in several lobes) was registered in 28.1% of the patients.

An analysis was made of the relationship between PTB aspects (according to case classification) and ventilation parameters that reflect the severity of obstructive disorders. FEV_1 was reduced in all groups, with 54.1% ± 11.35%, 55.5% ± 14.69%, and 44.9% ± 16.9% d.v. in the new case, relapse, and chronic PTB groups, respectively. The difference between the groups was not significant ($F = 1.18$, $p = 0.33$). The residual volume of the lungs was moderately increased in these groups, with 137.4% ± 36.60%, 148.9% ± 28.85%, and 144.1% ± 73.56% d.v., respectively; however, no differences were noted between the groups ($F = 0.17$, $p = 0.91$). The total lung capacity was within the conventional norm in all groups, with 99.4% ± 13.79%, 106.6% ± 15.79%, and 91.7% ± 18.02% d.v., respectively ($F = 2.05$, $p = 0.12$).

In all subgroups, patients with moderate and severe COPD predominated (according to spirometric classification), with 72.2% and 16.7% in the new case group, 90.0% and 0.0% in the relapse group, and 33.3% and 33.3% in the chronic TB group, respectively ($\chi^2 = 10.03$, $p = 0.347$). Thus, no difference in COPD severity was noted between the groups.

An acute test with GB was assessed (before and 15 min after inhalation), and the dynamics of ventilation parameters was studied after 30 and 120 min, as well as after 23 h 45 min. The results of the statistical analysis are presented in Table 2.

A single inhalation of 50 μg of GB resulted in improvements during the day in most ventilation and bronchial patency parameters (Table 2). A clinically significant (more than 12% of baseline) increase in FEV_1 was noted after 15 minutes. After 30 minutes, the improvement of FEV_1 increased and reached its maximum after 120 minutes. The increase in FEV_1 persisted the next day after 23 hours and 45 minutes from the inhalation.

Similar changes were detected for PFR and MFR_{50} (Table 2). The changes in PFR increased from 15 to 120 minutes from +9.2% to +22.1% and remained positive the next day (+10.9%). The changes in MFR_{50} during the day were more than 15% of the baseline, at +42.0%, +23.3%; +37.1%, and +21.0% after 15, 30, 120 min, and 23 h 45 min, respectively.

The increase in FVC parameters during the day was +17.5%, +17.3%, +20.5%, and +6.36% after 15 min, 30 min, 120 min, and 23 h 45 min, respectively, which may be due to the normalization of the total lung capacity following a decrease in the RLV, which means a decrease in the severity of the "trapped air" (Table 2).

As regards the effect of GB during the treatment course (1–3 months), positive changes in both parameters associated with bronchial patency (FEV_1, PFR, and MFR_{50}) and FVC were noted (Table 2). After 1, 2, and 3 months of GB treatment, the change rates were +13.1%, +9.3%, and +11.7% for FEV_1; +16.5%, +14.1%, and +20.8% for PFR; +12.8%; +16.16%, and +21.8% for MFR_{50}; and +12.78%; +5.77%, and +6.12% for FVC, respectively.

Thus, both during day 1 after GB inhalation and after 2–3 months of the treatment course, a clinically significant improvement in ventilation parameters was registered.

Changes in body plethysmography parameters were assessed (Table 3). The total airway resistance decreased 23 h 45 min after a single inhalation of GB on the next day with −18.5%, after 1 month with −15.1%, and after 3 months with −16.5% of the treatment course. A decrease in the RLV as a result of a decrease in the "trapped air" was recorded 23 h 45 min after GB inhalation on day 30 (−16.8%) and day 90 (−11.2%). Changes in total airway resistance and RLV were associated with the bronchodilator effect of GB.

Changes in total lung capacity after 24 h, 30 days, 60 days, and 90 days of the treatment course were insignificant (Table 3), which could be due to the multidirectional nature of the influence of both GB and morphological changes in the lung tissue on this parameter during chemotherapy.

A statistical analysis of the correlation of ventilation indicators at different time points was performed. A significant positive correlation was noted between changes in FEV_1 15 min after a single inhalation of GB on day 1 with the changes in FEV_1 after 30 min ($r = +0.912$; $p = 0.0001$), after 120 min ($r = +0.913$; $p = 0, 0001$), after 23 h 45 min on day 2 ($r = +0.578$; $p = 0.009$), and after 1 month of treatment with GB ($r = 0.688$; $p = 0.001$).

The quality of life of patients was evaluated according to CAT, SF-36, and SGRQ at baseline and after 3 months of GB treatment.

The initial (before GB treatment) values of the SF-36 quality of life domains the total group was different from the population values in Russia [14], namely, 63.9 ± 26.3 points (77.0 in Russia) for physical functioning, 48.6 ± 42.5 (53.8 in Russia) for role

Table 2. Initial values and changes over time in spirometry parameters after inhalation of 50 μg of glycopyrronium bromide in patients with pulmonary tuberculosis associated with chronic obstructive pulmonary disease (Student's *t*-test, pairwise comparison).

Parameter	FVC, L, M ± SD	FEV_1, L, M ± SD	PFR, l/s, M ± SD	MFR_{50}, l/s, M ± SD
Baseline, before glycopyrronium bromide (*n* = 38)	3.13 ± 0.68	1.79 ± 0.49	4.00 ± 1.13	1.16 ± 0.57
After 15 min (*n* = 38)	3.66 ± 1.042*	2.04 ± 6.98*	4.28 ± 1.28	1.60 ± 0.75*
Changes in relation to the baseline, %	+17.53 ± 30.1	+15.2 ± 13.93	+9.21 ± 23.18	+42.04 ± 35.29
t, p	t = 3.87. p = 0.0004	t = 7.48. p = 0.0001	t = 2.29. p = 0.027	t = 7.51. p = 0.00001
After 30 min (*n* = 38)	3.66 ± 1.02*	2.08 ± 0.52*	4.43 ± 1.24	1.41 ± 0.71*
Changes in relation to the baseline, %	+17.36 ± 0.28	+18.35 ± 16.82	+13.15 ± 21.2	+23.29 ± 35.29
t, p	t = 4.09. p = 0.0002	t = 7.37. p = 0.0001	t = 4.02. p = 0.003	t = 3.34. p = 0.002
After 120 min (*n* = 38)	3.76 ± 1.04	2.16 ± 0.55*	4.78 ± 1.23	1.55 ± .79*
Changes in relation to the baseline, %	+20.54 ± 29.79	+22.8 ± 17.7	+22.08 ± 21.89	+37.07 ± 39.18
t, p	t = 4.73. p = 0.0001	t = 9.04. p = 0.0001	t = 7.69. p = 0.0001	t = 5.154. p = 0.00001
After 23 h 45 min (*n* = 38)	3.31 ± 0.74*	1.96 ± 0.47*	4.39 ± 1.28	1.35 ± 0.54*
Changes in relation to the baseline, %	+6.36 ± 12.71	+11.24 ± 10.94	+10.95 ± 15.99	+21.0 ± 26.17
t, p	t = 2.99. p = 0.005	t = 6.5. p = 0.0001	t = 4.02. p = 0.0003	t = 4.47. p = 0.0001
Baseline	3.10 ± 0.69	1.73 ± 0.45	3.94 ± 1.09	1.07 ± 0.40
After 1 month (*n* = 27)	3.50 ± 0.93*	1.93 ± 0.49*	4.46 ± 1.17	1.16 ± 0.49
Changes in relation to the baseline, %	+12.78 ± 19.24	+13.1 ± 19.17	+16.48 ± 28.35	+12.85 ± 34.23
t, p	t = 3.56. p = 0.0014	t = 3.73. p = 0.0009	t = 3.31. p = 0.003	t = 1.32. p = 0.19
Baseline	3.19 ± 0.73	1.82 ± 0.39	4.13 ± 1.02	1.14 ± 0.39
After 2 months (*n* = 21)	3.39 ± .89*	1.99 ± 0.45*	4.67 ± 1.19	1.32 ± 0.52*
Changes in relation to the baseline, %	+5.77 ± 9.49	+9.3 ± 6.62	+14.08 ± 15.51	+16.16 ± 21.79
t, p	t = 3.05. p = 0.006	t = 5.95. p = 0.0001	t = 3.80. p = 0.001	t = 3.25. p = 0.004
Baseline	3.26 ± 0.69	1.84 ± 0.37	4.17 ± 1.01	1.12 ± 0.36
After 3 months (*n* = 19)	3.47 ± .87*	2.05 ± 0.50*	4.95 ± 1.30	1.35 ± 0.57*
Changes in relation to the baseline, %	+6.12 ± 9.91	+11.68 ± 14.79	+20.76 ± 25.05	+21.8 ± 29.0
t, p	t = 2.54. p = 0.02	t = 3.14. p = 0.006	t = 3.30. p = 0.004	t = 2.94. p = 0.009

Note: FVC, forced vital capacity of the lungs; FEV_1, forced expiratory volume per 1 s; PFR, peak flow rate; MFR_{50}, maximum flow rate at FVC 50%.

functioning due to physical condition, 75.5 ± 28.4 (61.3 in Russia) for pain intensity, 53.0 ± 19.1 (56.5 in Russia) for the general well-being, 61.5 ± 21.1 (55.1 in Russia) for vital activity, 75.7 ± 29.5 (69.7 in Russia) for social functioning, 43.2 ± 45.7 (57.2 in Russia) for role functioning due to the emotional state, 68.7 ± 17.0 (58.8 in Russia) for mental health, 48.9 ± 5.9 for the physical component of health, and 53.2 ± 9.6 points for the mental aspect of health.

The aspects of the quality of life according to the SGRQ in total group were below the norm, with 51.5 ± 19.65 for symptoms (normal, 9–15), 50.6 ± 21.44 for activity (physical) (normal, 7–12), and 36.1 ± 23.85 for influence (negative effect on the emotional state) (normal, 5–7).

During the GB treatment, the quality of life of the patients with COPD-associated PTB improved in most parameters. The total CAT score

Table 3. Baseline and changes in body plethysmography parameters after 23 h 45 min, 30 days, 60 days, and 90 days of inhalation of 50 μg of glycopyrronium bromide once a day in patients with pulmonary tuberculosis associated with chronic obstructive pulmonary disease (Student's t-test, pairwise comparison)

RF parameter	Raw tot, kPa/l/s	TLC, L	RLV, L
Baseline	0.236 ± 0.129	6.25 ± 1.06	2.65 ± 0.08
After 23 h 45 min (n = 37)	0.184 ± 0.115	6.24 ± 1.10	2.72 ± 0.80
Changes in relation to the baseline, %	−18.53 ± 24.88	+0.51 ± 0.12	−0.16 ± 29.76
t, p	t = 6.4. p = 0.0001	p = 0.95	p = 0.65
Baseline	0.272 ± 0.170	6.35 ± 1.14	2.87 ± 0.90
After 1 month (n = 27)	0.221 ± 0.146	6.23 ± 1.17	2.41 ± 1.12
Changes in relation to the baseline, %	−15.17 ± 25.56	−1.56 ± 9.05	−16.84 ± 28.19
t, p	t = 3.01. p = 0.006	p = 0.34	t = 3.51. p = 0.002
Baseline	0.231 ± 0.111	6.23 ± 1.13	2.73 ± 0.65
After 2 months (n = 21)	0.196 ± 0.074	6.37 ± 1.15	2.52 ± 0.90
Changes in relation to the baseline, %	−10.0 ± 29.02	+3.04 ± 13.8	−3.5 ± 42.31
t, p	t = 1.96. p = 0.06	p = 0.44	p = 0.36
Baseline	0.231 ± 0.067	6.35 ± 1.12	2.78 ± 0.65
After 3 months (n = 19)	0.164 ± 0.060	6.31 ± 1.14	2.46 ± 0.73
Changes in relation to the baseline, %	−16.55 ± 36.68	−0.41 ± 8.21	−11.2 ± 18.27
t, p	t = 3.08. p = 0.006	p = 0.74	t = 2.59. p = 0.018

Note: RF, respiratory function; Raw tot, total airway resistance; TLC, total lung capacity; RLV, residual lung volume.

after 3 months of GB treatment decreased by 7.0 points from 12.15 ± 6.62 (baseline) to 5.15 ± 4.63 (t = −5.35, p = 0.0001) and became below the meaningful threshold of 10 points. The mental health domain of the SF-36 questionnaire after 3 months of GB treatment increased by 9.2 points from 46.97 ± 9.92 (baseline; n = 19) to 56.13 ± 5.61 (after 3 months of treatment; t = 3.91, p = 0.001). Moreover, the positive dynamics of the physical health domain in the SF-36 questionnaire after 3 months was not significant [+3.5; 46.5 ± 8.4 (n = 19) and 49.9 ± 7.76 points, respectively (t = 1.69, p = 1.67)].

After 3 months of GB treatment, an improvement in the quality of life was noted for all aspects of the SGRQ questionnaire. The severity of symptoms decreased by 21.7 points, namely, 49.2 ± 20.95 (n = 17) at baseline and 27.4 ± 13.42 after 3 months (t = −5.9, p = 0.0001). The index of decrease in physical activity decreased by 14.8 points, namely, 46.6 ± 18.99 (n = 17) at baseline and 31.7 ± 14.57 after 3 months (t = −6.5, p = 0.0001). The indicator of negative effect on the emotional state decreased by 18.2 points, namely, 34.4 ± 21.67 (n = 17) at baseline and 16.2 ± 21.19 after 3 months (t = −3.49, p = s0.003).

Discussion

The problem of comorbidity in PTB is very relevant. Along with HIV infection, chronic viral hepatitis, coronary heart disease, diabetes mellitus, and COPD are the most frequently diagnosed comorbidities [3]. In patients with PTB, the presence of COPD not only aggravates the existing symptoms (cough and asthenia), but also leads to the development of respiratory failure and a decrease in exercise tolerance [5].

The specificity of BOS in COPD-associated PTB is that chronic PTB relapse leads to the development of bronchial obstruction, thereby exacerbating obstructive disorders caused by COPD [5]. The clinical structure of the study group fully reflects this dependence, and patients with newly diagnosed PTB (47.4%), with BOS caused mainly by COPD, were equally represented by chronic PTB (23.7%) and relapse (26.3%), which became a factor in BOS development.

The analysis justified the diagnosis of COPD, as the FEV_1/FVC parameter after the test using a bronchodilator was <70%, and the average smoker index for the group was >30 (30.9), which indicated a high risk of not only COPD but also of oncological diseases. The average patient age

was >50 years (51.3 years), which is also typical for COPD [13]. Among patients with moderate COPD (68.4%), those with type B predominated. High-resolution computed tomography detected emphysema in approximately 78% of cases, which, along with fibrotic and infiltrative changes in the lungs, decreased the diffusion capacity of the lungs (52.3% d.v.).

We used GB in the bronchodilator therapy, as early studies have shown its efficiency in patients with COPD [12], and the possibility of prescribing long-acting anticholinergics as monotherapy is presented in the clinical recommendations of the Russian Respiratory Society [13].

A study of the dynamics of the RF parameters showed that GB in patients with COPD-associated PTB had a similar effect on the state of bronchial patency, as in patients with COPD without PTB [12]. GB was effective in the acute test, and the increase in FEV_1 after 15 min (+15.2%) and 30 min (+18.3%) was higher than 12% of the baseline. This effect peaked after 120 min (22.8%) and was clinically significant after 23 h 45 min (+11.24%). We also found the effect of long-term use of GB, with +9.3% and +11.7% after 2 and 3 months of treatment, respectively. The results of this study confirm previously published data on the efficacy and nature of the action of GB in patients with COPD [11].

Body plethysmography parameters significant for diagnostics of bronchial obstruction also responded positively to GB treatment. Thus, after 1 and 3 months, a significant decrease was found in both total airway resistance (−15.17 and −16.55%, respectively) and RLV, namely, the severity of the "trapped air" (−16.84% and −11.2 %, respectively).

The positive effect of GB was proven by analyzing not only its effect on the RF parameters but also on the parameters of the quality of life and CAT results, which is also consistent with previously published data [11]. After 3 months of GB treatment, a clinically significant change in the severity of COPD symptoms was noted as a decrease in the total CAT score (−7.0 points) below the threshold of 10 points (negative effect of COPD on patient health). There was also an improvement in the quality of life according to SGRQ with a decrease in COPD symptoms (−21.7), physical activity (−14.8), and negative effect of COPD on the emotional state (−18.2).

Conclusions

1. A single inhalation of 50 μg of GB in patients with COPD-associated PTB had a beneficial effect during the day on the parameters of external respiration.

2. The course of treatment with 50 μg of GB once a day for 1–3 months in patients with COPD-associated PTB led to an improvement in bronchial patency.

3. GB treatment resulted in the improvement of body plethysmography parameters.

4. The results of the questionnaire survey showed that GB had a positive effect on the quality of life of patients with COPD-associated PTB.

5. GB can be recommended for the treatment of patients with COPD-associated PTB.

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Author details

Marat F. Yaushev, MD, D.Sc. (Med.), Prof., Depart. of Phthisiopulmonology, Kazan State Medical University, Russia; umukgmu@rambler.ru; ORCID: http://orcid.org/0000-0001-6485-3166

Alexey P. Alexeev, Chief Physician, Tatarstan Republican Clinical Anti-Tuberculosis Dispensary; guz.rkpd@tatar.ru; ORCID: http://orcid.org/0000-0001-5334-2133