ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2005; 25 (4): 257-264
1173-2563/05/0004-0257/$34.95/0

Efficacy of Supplemental Anti-Inflammatory Therapy with Fenspiride in Chronic Obstructive and Nonobstructive Bronchitis

L.I. Volkova,[1] *A.A. Budkova,*[1] *N.N. Filonova,*[1] *E.I. Khristolyubova,*[1] *E.B. Kutuzova,*[1] *N.V. Koroleva,*[1] *T.T. Radzivil,*[1] *Z.R. Aminova*[1] and *A.G. Chuchalin*[2]

1 Siberian Medical University, Tomsk, Russia
2 Pulmonology Research Institute, Russian Federation Ministry of Health, Moscow, Russia

Abstract

Objective: The objective of this randomised, nonblind study was to assess the efficacy of fenspiride as complementary anti-inflammatory therapy in combination with ipratropium bromide in patients with chronic bronchitis (CB). A comparison was made with ipratropium bromide alone, the generally accepted standard therapy for CB.

Methods and subjects: The study population comprised 20 patients with chronic obstructive bronchitis (COB) and 60 patients without signs of obstruction. Fifty-one males (64%) and 29 females (36%) aged from 25 to 65 years were studied over a 6-month treatment period. Combined therapy with fenspiride (160 mg/day) and ipratropium bromide (160 μg/day) was prescribed to 39 patients (28 with CB and 11 with COB) for 6 months, and monotherapy with ipratropium bromide (160 μg/day) was prescribed for 41 patients (32 with CB and nine with COB).

Results: The combined therapy group had a reduced intensity of dyspnoea, improvements in sputum nature and quantity of exudation, and a reduced intensity of coughing. The monotherapy group showed reductions in sputum exudation and cough intensity. Improvements in lung respiratory function were observed in both groups, but were greater in the combined therapy group of patients. Reduced cytosis, percentage and absolute content of neutrophils, and absolute content of lymphocytes and eosinophils in induced sputum were observed with CB patients in the combined therapy group. A reduced content of lymphocytes and an increase in macrophages were observed with CB patients in the monotherapy group. A significant decline in tumour necrosis factor (TNF)-α content in sputum was observed with both therapeutic regimens, although a statistically significant decline in serum TNFα (10.85 ng/L to 5.58 ng/L; $p = 0.03$) and reduced interleukin-8 in sputum (311.94 ng/L to 122.02 ng/L; $p = 0.027$) were observed with patients given combined therapy.

Conclusion: The study showed greater efficacy of long-term treatment with fenspiride and ipratropium bromide compared with ipratropium bromide alone in patients with CB. This combination regimen can be recommended for the reduc-

tion of inflammation and prevention of disease progression in patients with CB and may also be useful in patients with COB.

The modern approach to the pathogenesis of both obstructive and nonobstructive bronchitis regards inflammation as the driving mechanism.[1] Clinical symptoms of the disease and lung function disturbance reflect this inflammation process to some extent. Insufficient therapeutic efficacy in chronic bronchitis (CB) is related to the limited anti-inflammatory activity of traditionally prescribed medications (β_2-agonists, anticholinergics, methylxan-thines, inhaled glucocorticosteroids, mucolytic [mucokinetic, mucoregulator] agents, and antibiotics). Fenspiride is of interest for the treatment of CB because its anti-inflammatory action inhibits synthesis of proinflammation mediators – prostaglandins and leukotrienes. The drug prevents formation of arachidonic acid from phospholipids of cell membranes by blocking A_2 phospholipase,[2,3] and reduces migration of inflammation cells through the diminished formation of chemotaxis factors. It also inhibits products of certain mediators secreted by respiratory tract cells (particularly the release of tumour necrosis factor [TNF]-α), blocks histamine H_1-receptors, and inhibits α_1-adrenoreceptors, through which the secretion of viscous mucus is stimulated. This generally results in reduced inflammation of the airways.[4] Consequently, the degree of airways obstruction diminishes and the quantity of exuded sputum decreases. Fenspiride has a positive effect on mucociliary escalation and speed of mucociliary transport.[1]

Some clinical studies have demonstrated the efficacy of fenspiride in the treatment of chronic obstructive bronchitis (COB).[1,5-9] The presence of persisting bronchial inflammation is also characteristic of all stages of CB. It is known that mucociliary transport is materially affected in CB patients, even at the initial development stage. Fenspiride administration is therefore suitable for CB patients experiencing coughing and sputum exudate.[9]

This study assessed the efficacy of oral fenspiride as complementary anti-inflammatory therapy in combination with oral ipratropium bromide in patients with CB and COB. This was performed in comparison with patients receiving the generally accepted standard treatment of ipratropium bromide alone.[4]

In addition, we studied the effect of fenspiride on a variety of respiratory symptoms including frequency and severity of acute exacerbations, respiratory function and cellular composition of induced sputum (IS) and its TNFα and interleukin-8 (IL-8) content.

Materials and Methods

This randomised, nonblind, parallel group study included 80 patients with CB in clinical remission, who were aged from 25 to 65 years (mean 44.2 years). The study population was a random sample that included 51 males (64%) and 29 females (36%). Sixty-two were smokers, six were former smokers, and 12 were non-smokers.

Study inclusion criteria were: presence of generally accepted CB criteria (daily coughing with sputum lasting ≥3 months per year over ≥2 years); no history of suffocation episodes typical for bronchial asthma or other diseases accompanied by coughing and shortness of breath; and forced expiratory volume in 1 second (FEV_1) reversibility was <10% of the predicted value after inhaled β-agonist (salbutamol) test. Exclusion criteria were treatment with corticosteroids during the 2 months prior to visit 2, and nonspecific anti-inflammatory drugs during the 3 months prior to visit 2.

According to the GOLD criteria (global consensus on the definition, classification and management of chronic obstructive pulmonary disease [COPD][10]), 60 patients had stage 0 COPD (FEV_1 after bronchial spasmolytic test ≥80%) and 20 had stage 1–2 COPD (FEV_1 after bronchial spasmolytic test <80%). We identified patients with normal external respiration function indices as CB patients and those with obstructive disturbances as COB

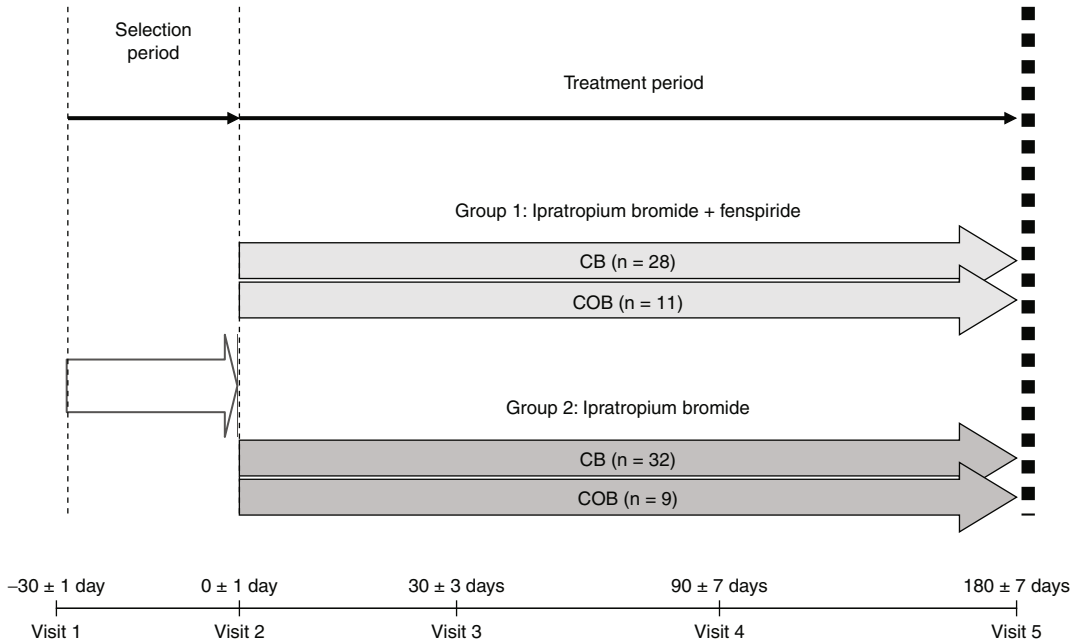

Fig. 1. Diagrammatic representation of the study design. **CB** = chronic bronchitis; **COB** = chronic obstructive bronchitis.

patients. Patients were randomised into two groups according to a 1 : 1 ratio: group 1 comprised 39 patients (28 with CB and 11 with COB) and group 2 comprised 41 patients (32 with CB and nine with COB).

All patients provided signed informed consent to participate in the study, and approval from the Institutional Review Board was received.

Study Design

The study design is shown in figure 1. A form indicating presence of respiratory symptoms and earlier diagnosed CB was completed during the first visit. Tests required for validation of this diagnosis were performed later and patients were observed over 1 month in order to eliminate the signs of acute exacerbation. Thus only patients in a stable state were included, as confirmed by the absence of exacerbation symptoms (measured according to classical Winnipeg criteria[4]) and no significant difference in spirometric values or tracings between visits 1 and 2. Starting at visit 2, combined treatment with fenspiride (Eurespal®, Servier, Paris, France)[1] at a daily dose of 160mg (80mg twice daily) and ipratropium bromide (Boehringer Ingelheim Pharma GmbH, Austria) at a daily dose of 160µg was prescribed to patients in group 1 for 6 months. Ipratropium bromide monotherapy at the same doses was prescribed to patients in group 2.

The study design included a numerical score from 1 to 4, one point for each of the major CB clinical symptoms: coughing, sputum (its nature and differences with exudation) and dyspnoea. Patients recorded these symptoms every week over 6 months of treatment, while the physician assessed them during each visit. The physician also examined the patient at each visit, recorded the number of administered tablets, ipratropium bromide doses administered and any adverse effects observed in the course of treatment. All major clinical and laboratory data were entered on the registration card of each patient. Respiratory function indices were determined using a portable minispirometer (VM1; Clement Clarke

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Inc., London, UK) at each visit. IS was gathered and its cytological composition studied at visits 2, 4 and 5. IS and blood were tested for content of the inflammatory cytokines TNFα and IL-8 at visits 2 and 5. Blood tests, ALT and AST levels and serum creatinine content were also performed at visits 2 and 5.

IS collection was performed after inhalation of 3–5% NaCl solution through an ultrasonic nebuliser over 5–7 minutes. Sputum was processed and analysed no later than 2 hours after its production. Processing consisted of incubation with a 0.1% solution of dithiotreitiol (DL) below 37°C over 15 minutes, centrifugation, preparation of smears from the settlement with Romanovsky's stain, and production of supernatant for TNFα determination. Supernatant was prepared without DL addition when IL-8 was determined in sputum. Cells were counted using light microscopy under immersion. Cytosis was studied using a Gorjaev count chamber. Five millilitres of venous blood was collected to determine cytokine content in serum, which was later centrifuged for serum production.

Cytokines (IL-8 and TNFα) were determined by immunoenzyme assay (IEA) [CytImmune Kits, College Park, MD, USA].

Statistical Analyses

Results were analysed using the STATISTICA 5.0 (Statsoft, Inc., Tulsa, OK, USA) statistical computer program. Statistical hypotheses were tested at the 0.05 significance level for two-sided criteria. Pearson's chi-squared (χ^2) criterion was used to analyse comparability of groups at the initial level. Repeated measurements of clinical parameters were compared in each group by Friedman's nonparametric method of multiple comparisons. The Newman-Castle criterion was used for paired comparisons in cases of significant changes of the given indices. Repeated measurements of functional and laboratory parameters for separate pairs of visits were performed using Wilcoxon's nonparametric criteria of paired comparisons. The absolute variation value of the index was also calculated. Average values of functional and laboratory parameters between groups 1 and 2 were compared at different visits by means of the Mann-Whitney non-parametric criteria.

Results

Patient Distribution

The distribution of patients in groups at the second visit (V2) was found to be homogenous by age ($p < 0.05$), sex and smoking ($p < 0.01$), and by intensity of CB respiratory symptoms (coughing, sputum properties, nature of exudation and dyspnoea [$p < 0.05$]). According to laboratory and instrumental studies, groups were also homogenous and comparable, with the only exception being the IL-8 level in sputum, which was consistently higher in group 1 (311.94 ± 146.44 ng/L) compared with group 2 (106.39 ± 68.44 ng/L, $p = 0.005$). No differences were found in the average value of spirometric readings, based on the FEV_1 level prior to commencement of treatment. The two treatment groups were thus comparable.

Analysis of Efficacy

Efficacy of therapy was assessed in each group with regard to variations in respiratory symptoms, spirometric readings, IS cytology and proinflammatory cytokines in IS and blood. A clinical effect, measured as an aggregate of all respiratory symptoms, was observed with all patients in both groups. The analysis showed that a reduction in cough intensity ($p = 0.07$), significant reduction of dyspnoea ($p = 0.004$), sputum nature ($p = 0.015$) and its exudation ($p = 0.019$) was observed in all patients in the combined therapy group (group 1). The monotherapy patients (group 2) only showed a significant reduction in coughing intensity ($p = 0.02$) and sputum exudation ($p = 0.003$).

A significant improvement in lung function was observed in both groups. FEV_1 increased in the fenspiride group (visit 2: 86.85 ± 12.45%, visit 5: 91.38 ± 13.69%; $p = 0.006$), while forced vital lung capacity (FVLC) rose in the monotherapy group (visit 2: 93.5.14 ± 19.04%, visit 5: 101.3 ± 16.08%; $p = 0.002$). These are the average values for COB and CB patients combined, and are detailed in figure

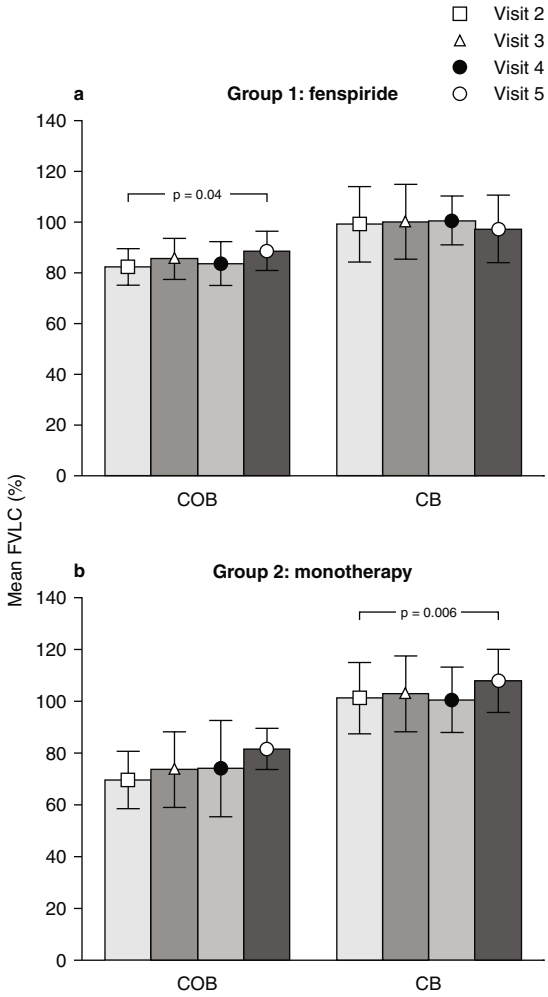

Fig. 2. Percentage forced vital lung capacity (FVLC) of patients in (**a**) group 1 (fenspiride plus ipratropium bromide) and (**b**) group 2 (ipratropium bromide alone) during the treatment period. Values are given as mean ± SD. **CB** = chronic bronchitis; **COB** = chronic obstructive bronchitis.

2 and figure 3. The figures show the mean values of the indices from visit to visit for patients in both groups, categorised according to FEV_1 level prior to commencement of treatment. Increases in both FVLC and FEV_1 were observed at visit 5 in COB patients in the fenspiride group. FVLC increased for CB patients in the monotherapy group.

IS cytological studies demonstrated a higher number of neutrophils and a lower content of macrophages in both groups in comparison with healthy individuals.[11-13] Variations in cellular composition of IS during therapy are shown in table I and table II. Significantly decreased cytosis, percentage and absolute content of neutrophils, lymphocytes and eosinophils were observed with CB patients in the fenspiride combined therapy group. An increase in macrophages and reduced growth of lymphocytes were recorded for CB patients in the monotherapy group.

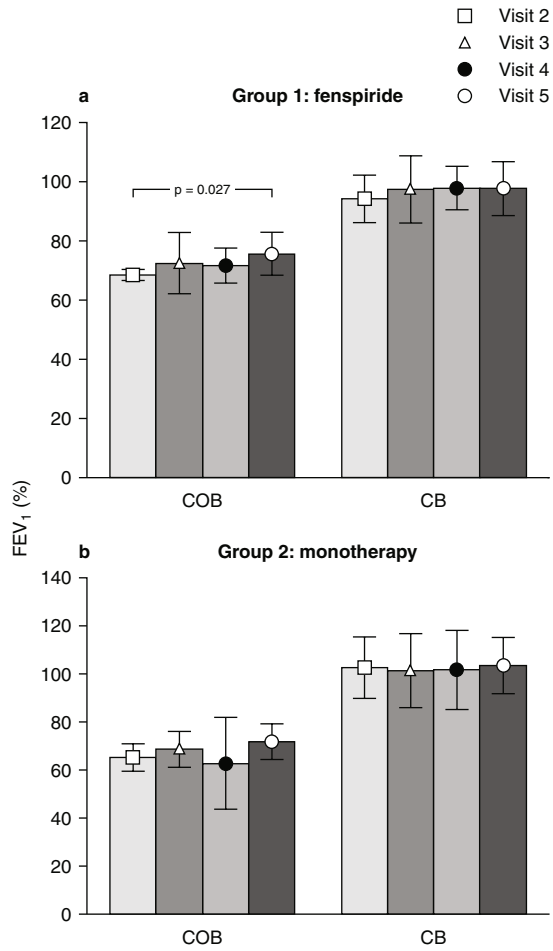

Fig. 3. Percentage forced expiratory volume in 1 second (FEV_1) of patients in (**a**) group 1 (fenspiride plus ipratropium bromide) and (**b**) group 2 (ipratropium bromide alone) during the treatment period. Values are given as mean ± SD. **CB** = chronic bronchitis; **COB** = chronic obstructive bronchitis.

Table I. Induced sputum cellular composition for patients receiving fenspiride in combination with ipratropium bromide (group 1)[a]

Index	Chronic bronchitis (n = 18)			Chronic obstructive bronchitis (n = 8)		
	initially	after 6 months	p-value	Initially	after 6 months	p-value
Cytosis ($\times 10^6$/L)	2.05 (1.0–4.5)	1.37 (0.70–2.50)	0.05	2.44 (0.8–4.0)	2.93 (1.4–4.5)	>0.05
Neutrophils (%)	81.14 (49.50–90.75)	64.85 (33.25–74.00)	0.01	83.30 (75.25–90.00)	78.75 (55.25–90.50)	>0.05
Neutrophils ($\times 10^6$/L)	2.00 (0.19–5.43)	0.97 (0.36–2.06)	0.006	1.59 (0.48–2.79)	1.480 (0.35–3.62)	>0.05
Lymphocytes ($\times 10^6$/L)	0.09 (0.00–0.58)	0.04 (0.00–0.20)	0.05	0.01 (0.00–0.039)	0.004 (0.00–0.027)	>0.05
Eosinophils ($\times 10^6$/L)	0.17 (0.00–0.98)	0.09 (0.00–0.41)	0.005	0.07 (0.00–0.33)	0.05 (0.00–0.154)	>0.05

a Mean value of indices and spread (minimum and maximum values) are presented.

Determination of cytokines in sputum and serum prior to therapy initiation demonstrated that TNFα was present in serum in 44 of 63 patients (69.8%) and in sputum in 53 of 63 patients (84.1%). IL-8 was present in serum in 43 of 63 patients (68.2%) and in sputum in all 19 patients investigated. It is assumed that these cytokines should not be present in normal conditions; therefore, their presence in the majority of our patients may be viewed as a pathological event. Low IL-8 content in serum versus high values in sputum (0.35 and 269.68 ng/L, respectively) probably reflects a particular action of this cytokine and its significance in local inflammatory reactions.

Cytokines were determined during visit 5 in a smaller number of patients, since some had withdrawn from the study at visit 4, while it was not possible to induce sputum in all patients. Statistical significance is shown in table III. TNFα in sputum consistently declined in both groups. As far as TNFα in serum and IL-8 in sputum are concerned, a statistically significant decrease was observed in combination therapy recipients (group 1) only. CB patients prevailed in each group, and variations in cytokine content were assessed at visits 2 and 5. The analysis demonstrated a consistent, statistically significant reduction of indices in both groups, which correlated with an improvement in clinical efficacy.

Adverse Events

Adverse events related to fenspiride were observed in five patients from group 1 (12.8%) during the initial days of therapy (bitter taste, heaviness or pains in right hypochondrium, drowsiness and headache). However, these events disappeared quickly and the decision to stop the drug due to persistent headache was made for one female patient only. No adverse events were observed in group 2. No patient showed negative changes in transaminases, creatinine levels or blood picture at visit 5.

The study was completed by 28 patients (71.8%) in group 1 and 30 patients (73.2%) in group 2. Excluded patients comprised CB patients who independently changed their drug therapy regimen after respiratory symptoms disappeared or diminished.

Three patients receiving ipratropium bromide monotherapy experienced exacerbations within the period of study, which necessitated antibacterial therapy. No exacerbations occurred with patients taking fenspiride during the same period. Four patients in group 1 and three patients in group 2 had viral respiratory infections within the period from visit 3 to visit 4. No prescription of antibiotics was necessary, although their doctors had always previously prescribed antibacterial drugs in such cases prior to inclusion into the study.

Table II. Induced sputum cellular composition for patients receiving ipratropium bromide monotherapy (group 2)[a]

Index	Chronic bronchitis (n = 19)			Chronic obstructive bronchitis (n = 6)		
	initially	after 6 months	p-value	initially	after 6 months	p-value
Macrophages (%)	12.18 (4.0–37.50)	26.23 (4.25–61.50)	0.001	12.25 (8.00–18.25)	14.3 (5.75–26.25)	>0.05
Lymphocytes ($\times 10^6$/L)	0.06 (0.00–0.16)	0.03 (0.00–0.13)	0.02	0.023 (0.01–0.06)	0.033 (0.00–0.13)	>0.05

a Mean value of indices and spread (minimum and maximum values) are presented.

Table III. Cytokines in sputum and blood serum of patients at visits 2 and 5 (mean ± SD)

Index (ng/L)	Group 1			Group 2		
	visit 2	visit 5	p-value	visit 2	visit 5	p-value
TNFα in sputum	26.59 ± 5.67 (n = 21)	7.83 ± 3.11 (n = 21)	0.007	25.63 ± 3.75 (n = 21)	1.63 ± 0.40 (n = 21)	0.001
TNFα in serum	10.85 ± 1.96 (n = 16)	5.58 ± 3.69 (n = 16)	0.03	11.87 ± 1.91 (n = 11)	11.14 ± 8.82 (n = 11)	>0.05
IL-8 in sputum	311.94 ± 68.1 (n = 9)	122.02 ± 22.5 (n = 9)	0.027	106.39 ± 30.60 (n = 9)	59.66 ± 11.85 (n = 9)	>0.05

IL-8 = interleukin-8; **TNF**α = tumour necrosis factor-alpha.

Discussion

This study demonstrated that a change in composition of induced sputum is present with the majority of CB and COB patients even in a stable condition. This is primarily expressed as a meaningful increase in neutrophils and higher IL-8 and TNFα content in sputum and serum compared with controls. There is also evidence for a higher content of inflammatory cells and proinflammatory cytokines in sputum and blood during acute exacerbations of COB and in patients with a stable condition compared with controls.[14-17] Cytokines are important regulators of inflammation; sufficient evidence indicates that a high level of proinflammatory cytokines is an adverse factor in the degree of activity and severity of the pathological process.[18-20] Changes in the level of cytokines and sputum cellular composition indicators may be used for assessment of treatment efficacy.[21] In the opinion of many researchers, these indices reflect both the inflammatory process activity and evidence of its persistent course.[22,23] The presence of this inflammatory process is largely connected with the progressive course of bronchitis and this justifies anti-inflammatory therapy for such patients.

Long-term ipratropium bromide therapy is at present the accepted standard therapy for CB patients.[4] According to our data, a combination of ipratropium bromide and fenspiride provides better clinical efficacy than ipratropium bromide therapy alone. Combined therapy was accompanied by a decreased intensity in dyspnoea, reduction in sputum nature and exudation, and a reduction in coughing intensity. Monotherapy was associated with a reduction in sputum exudation and coughing intensity. Lung ventilation function improved in both groups, albeit manifested to a larger degree in the group of patients given combined therapy. The fact that FEV_1 significantly increased only in group 1 patients who had experienced its decline prior to commencement of treatment was probably a result of reduced inflammation and its associated reversible bronchial obstruction component under fenspiride therapy.

IS cellular composition variations were noted with both regimens. The degree of significant reduction of cytosis and the number of neutrophils in IS was achieved in the combined therapy group only.

The combination of traditional therapy and fenspiride resulted in reduced TNFα levels in sputum and serum and reduced IL-8 levels in sputum, which were not observed in patients receiving ipratropium bromide monotherapy. A TNFα decline in sputum in the monotherapy group was probably related to the spontaneous reduction in intensity of chronic inflammation, since ipratropium bromide alone does not have significant anti-inflammatory activity.

Conclusion

This study demonstrated a greater efficacy of long-term combined therapy with fenspiride and ipratropium bromide compared with ipratropium bromide monotherapy in patients with CB. The addition of fenspiride can be recommended to reduce inflammation and prevent disease progression in CB patients without disturbances in respiratory function and can also be useful in patients with COB.

The study findings are of clinical importance since they propose an improved strategy for the long-term management of CB and COB, which may

also have a role in the prevention of disease progression in these patients.

Acknowledgements

Publication assistance was provided by Servier Russia.

The authors have no potential conflicts of interest that are directly relevant to the contents of this manuscript.

References

1. Bezlepko AV. Experience of long-term application of fenspiride (Eurespal) for treatment of patients with chronic obstructive bronchitis. Pulmonology 2002; 3: 76-82
2. Edvard Y, Kato G, Bodinier MC, et al. Fenspiride et inflammation en pharmacologie expérimentale. Eur Respir Rev 1991; 1 (2): 33-40
3. Pipy B, Pinelli E, Forgue MF, et al. Fenspiride inhibits arachidonic acid metabolite production and cytolic Ca2+ increase by inflammatory macrophages [letter]. Eur Respir J 1992; 5: 237
4. Carre PH, Pipy B, Pinelli E, et al. *In vitro* effects of fenspiride on the production of free oxygen radicals, prostaglandins and leukotrienes by guinea-pig alveolar macrophages. Eur Respir Rev 1991; 1 (2): 79-85
5. Volkova LI, Bukreeva EB, Boyarko VV, et al. Experience of fenspiride (Eurespal) application upon chronic bronchitis exacerbation. Clin Pharmacol Ther 2000; 5 (9): 65-8
6. Kunitsyna YL, Shmelev EI. Anti-inflammatory therapy of patients with chronic obstructive pulmonary disease. Pulmonology 2003; 2: 111-6
7. Ovcharenko SI. Anti-inflammatory therapy of chronic bronchitis. RMJ 2001; 9 (5): 20-4
8. Akoun G, Arnaud F, Blanchon F, et al. Effect du fenspiride sur la fonction respiratoire et gazométrie de patients présentant une bronchopathie chronique obstructive stable. Eur Respir Rev 1991; 1: 51-6
9. Oliveri D, Del Donno M. Etude de faction du fenspiridi (pneumorel 80 mg) sur la clairance mucociliare chez le, bronchitique chronique. J Intern Med 1987; 96: 395-8
10. Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO workshop report 2001; 3 (1)
11. Fahy JV, Liu J, Wong H, et al. Cellular and biochemical analysis of induced sputum: reproducibility and validity of cell and fluid-phase measurements. Am Rev Respir Dis 1993; 147: 1126-31
12. Lensmar C, Elmberger G, Sandgren P, et al. Leukocyte counts and macrophage phenotypes in induced sputum and bronchoalveolar lavage fluid from normal subjects. Eur Respir J 1998; 12: 595-600
13. Rutgers SR, Timens W, Kaufman HF. Comparison of induced sputum with bronchial wash, bronchoalveolar lavage and bronchial biopsies in COPD. Eur Respir J 2000; 15: 109-15
14. Konmlev AD, Kalinina NM, Sysoev KA, et al. Cytokine profile of patients with chronic obstructive pulmonary disease. Med Immunol 2002; 4 (1): 87-92
15. Bhowmik A, Seemungal T, Sapsford RJ, et al. Cytokines in induced sputum during exacerbations of chronic obstructive pulmonary disease. Thorax 2000; 55: 114-20
16. Keatings VM, Collins PD, Scott DM, et al. Differences in interleukin-8 and tumor necrosis factor in induced sputum from patients with chronic obstructive pulmonary disease or asthma. Am J Respir Crit Care Med 1996; 153: 530-4
17. Richman-Eisenstadt JB, Jorens PG, Hebert CA, et al. Interleukine-8: an important chemoattractant in sputum of patients with chronic inflammatory airway diseases. Am J Physiol 1993; 264: L413-8
18. Ketlinsky SA, Kalinina NM. Cytokines of mononuclear phagocytes in regulation of inflammation and immunity [letter]. Immunology 1995; 3: 15
19. Chereshnev VA, Gusev EY. Inflammation immunology: role of cytokines. Med Immunol 2001; 3 (3): 361-8
20. Linden M, Rasmussen JB, Pitulainen E, et al. Airway inflammation in smokers with nonobstructive and obstructive chronic bronchitis. Am Rev Respir Dis 1993; 148: 1226-32
21. Culpitt SV, de Matos C, Russell RE, et al. Effect of theophylline on induced sputum inflammatory indices and neutrophil chemotaxis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002; 165: 1371-6
22. Stockleu RA, Bauley DL. Validation of assays for inflammatory mediators in sputum. Eur Respir J 2000; 15: 779-81
23. Yamamoto C, Yoneda T, Yoshikawa M, et al. Airway inflammation in COPD assessed by sputum levels of interleukin-8. Chest 1997; 112: 505-10

Correspondence and offprints: Dr *L.I. Volkova*, Pulmonology Department, City Hospital No. 3, Nakhimov Street, Tomsk, 3, Russia.

