European Respiratory Society

European Respiratory Journal

VOLUME 28 | SUPPLEMENT 50 | SEPTEMBER 2006

Supported by an unrestricted educational grant from

NOVARTIS

Results: The median annual number of exacerbations per patient over the study period was 3, the mean (95%CI) annual number of hospital admissions was 0.75(0.3-1.1). Frequent exacerbators had significantly lower baseline FEV_1(%pred), higher MRC score and chronic respiratory symptoms at baseline. The mean annual change in FEV_1(%pred) overall was -2.8(2.5-3) corresponding to mean annual decline of -81ml. The average annual change in FEV_1(%pred) was significantly lower in those patients who experienced less or equal to 3 exacerbations per year [-1.1(-0.9, -1.3) versus -3.7(-3.5, -3.9), p=0.001)].

E303

Monocytes phagocytosis activity during remission and exacerbation of COPD

Julia A. Mikryukova, Gusein V. Ashyrov, Galina L. Ignatova, Larisa A. Stepanisheva, Aiman S. Sarsenbaeva. *Therapy and Phthysiopulmonology Dept., Ural State Medical Academy Posdyploma Education, Chelyabinsk, Russia*

Materials were over 80 men are included in the present research with diagnosis COPD at risk and COPD I-III stages meanage 54 years, some of them were workers of tractor plant and some living at this area. We had been carried out the analysis of activity monocyte phagocytoses during an aggravation and remission of process. The greatest activity of phagocytosis were characterized monocytes at patients with COPD during remission both in group of workers of a factors (44,66±2,67), and in group of the men living in area of this industrial enterprise (44,55±2,29). The lower level (34,38±4,50) of activity of monocytes phagocytosis has been fixed during an aggravation of disease at patients without dependence from a place of work and residing, and also during remission COPD at risk at persons with influence professional harm and without this factor. Paradoxical decreasing of activity of monocytes phagocytosis during an aggravation can be connected with reciprocated character of mutual relations of the basic phagocyte cells: granulocytes and monocytes. At carrying out of the correlation analysis interrelations have been revealed with relative quantity of lymphocytes in peripheral blood (r=0,59, p<0,05). This communication can be bilateral, on the one hand, the increase in quantity of lymphocytes can determine their greater effect on mononuclear phagocytes as a result of quantitative growth of production limphokines, influencing on migration, adghesive properties of cells, on the other hand, high phagocyte activity connected by activation of other functions of these cells (amplification of secretion IL-1, IL-6, etc.) can influence strengthening of processes of migration and lymphocyte proliferation, their quantity.

E304

Effects of tiotropium and salmeterol/fluticasone combination on lung hyperinflation, dyspnea and exercise tolerance in COPD

Pejman Golabi, Nurhayat Topaloglu, Sait Karakurt, Turgay Celikel. *Pulmonary Diseases and ICU, Marmara University Faculty of Medicine, Istanbul, Turkey*

It has been shown that patients with chronic obstructive pulmonary disease (COPD) develop dynamic hyperinflation (DH), which contributes to dyspnea and exercise intolerance. Tiotropium and Salmeterol/fluticasone combination (SFC) are medications used for maintenance therapy in COPD patients. The effects of tiotropium on DH are well known, whether the effects of SFC has not been assessed.
The aim of the present study was to compare the long term effects of tiotropium 18 μg daily with SFC 50/500 μg two times a day, on forced expiratory volume in one second (FEV_1), inspiratory capacity (IC), forced vital capacity (FVC), exercise and dyspnea in COPD patients.
A cross-over, randomized study was carried out on 15 stable COPD patients. Patients underwent pulmonary function testing, six minute walk test and dyspnea evaluation with Borg scale in basal condition and four weeks after each medication. Tiotropium provided 288±96ml increase in FEV_1 (p<0.0001), 383±94ml increase in IC (p=0.001) and 54±7m increase in six minute walk distance (6MWD) (p<0.0001). SFC therapy provided 196±115ml increase in FEV_1 (P=0.013) and 214±74ml increase in IC values (p=0.012). 6MWD had improved by 38±8m after SFC therapy (p<0.0001). Significant decrease in Δ borg scores determined after both medications (p<0,0001).
The results indicate that, there was a significant increase in FEV1, IC, 6MWD and improvement of dyspnea sensation after both medications. Tiotropium resulted in more significant changes compared with SFC.
We concluded that comparing with SFC, four weeks of tiotropium therapy had greater effects on dynamic hyperinflation and exercise tolerance in stable COPD patients.

E305

Gram-negative enterobacteria in the etiological structure of COPD exacerbation

Elena Mishustina[1], Tatyana Ageeva[1], Sergey Mishustin[2]. *[1]Department of Internal Diseases, Military Medical Institute, Tomsk, Russia; [2]Health Department, Tomsk Oblast Administration, Tomsk, Russia*

330 patients with COPD exacerbation were examined to identify etiological structures of bacterial COPD exacerbation and specific weight of gram-negative enterobacteria. Diagnosis and verification of exacerbation were based on the common criteria and COPD criteria including known methods of cytological and bacteriological tests: the criterion of etiological significance was a concentration of 10^6/ml bacteria and smaller microbe bodies in sputum. Bacteriological tests were performed repeatedly (initially – prior to the start of anti-bacterial therapy, continued– up to elimination of the agent in sputum). We identified that bacteriological agents of etiological significance were reported in 83% of cases; etiological structure of bacterial exacerbation: S.pneumoniae – 118 cases (36%), H.influenzae – 78 (24%), gram(-) enterobacteria – 63 (18%), Gram(-) enterobacteria associated with other bacteria – 9 (3%), S.aureus – 4 (1%); S.aureus in association with other bacteria – 3 (1%). A bacterial agent was not significantly identified in 55 patients (17%). Identification of predictably unfavorable microbe associations (gram(-) enterobacteria + staphylococcus) and high level of gram(-) enterobacteria in the structure of COPD exacerbation became a crucial fact.
Conclusions: In 83% of cases, COPD exacerbation is caused by bacterial agents with a determined structure and every forth patient has COPD exacerbation caused by gram(-) enterobacteria and/or pathogenic staphylococcus.

E306

Can treatment with tiotropium influence nitrate stress in the COPD patients?

Jaromir Musil, Jaroslav Chládek. *Pneumology Clinic, Charles University, 2nd Medical School, Prague, Czech Republic; Institute for Pharmacology, Charles University, Medical Faculty, Hradec Králové, Czech Republic*

The aim of our study was to ascertain if the treatment with tiotropium can diminish nitrate stress in stable COPD patients.
Twenty patients with COPD (11 men, 9 women, mean age 65,7 years) were examined. Twelve patients had COPD stage II, 8 COPD stage III. Concentrations of nitrite (NO_2) and nitrate (NO_3) were measured in exhaled breath condenstae (EBC). EBC was collected before start of therapy with tiotropium, after 4 and 12 weeks of treatment.
EBC samples were collected using a specially designed condensing chamber (EcoScreen, Jaeger, Germany). Nitrites and nitrates were assayed by ionex chromatography. Statistical analysis was performed by using Wilcoxon test for paired data and analysis of dispersion for repeated measurements.
Results: Results are shown in table below. We did not find any significant changes between concentration of nitrite (NO_2) measured before treatment and after 4 and 12 weeks of treatment with tiotropium. The concentration of nitrate (NO_3) after 12 weeks of treatment was significantly less than its concentration before starting treatment (p=0,010).

Parameters of nitrate stress measured in EBC

	before treatment	4th week	12th week
NO_2 (umol/l)	5.33	5.48 (NS)	3.33 (NS)
NO_3 (umol/l)	69.34	54.57 (NS)	33.87 (p=0,01)

Conclusion: The treatment with tiotropium can diminish nitrate stress in patients with COPD.

E307

The role bacterial and viral infection in COPD exacerbation

Emilija P. Pejovic, Ljiljana Kezunovic, Maja Batricevic, Nebojsa Kavaric. *Pulmology, Health Center, Podgorica, Montenegro, Serbia & Montenegro; Pediatric, Health Center, Podgorica, Montenegro, Serbia & Montenegro; Clinical Biochemy, Private Laboratory, Podgorica, Montenegro, Serbia & Montenegro; Pediatria, HC, Podgorica, Montenegro, Serbia & Montenegro*

Viral and bacterial infection is fundamental to the ethyology persistence COPD.
The study aimed to evaluate the role of bacterial and viral colonization on COPD natural history in stable patients Patients where threat for twelve month.
Total of 250 patients (57 females, mean age 65 plus-minus 7.1 yrs. FEV1 > 30% =32. FEV1 30-50% = 99. FEV1 > 50% =119.) with COPD exacerbation have been included.
One hundred and one patients (40,3%) presented viral evidence (Rhino virus, Influenza virus, RSV, Meta pneumo virus).
Sixty seven (27%) presented bacterial growth in sputum (H. influence, M. CAT., P.aeruginosa, Chlamidia, Mycoplasma, Legionella)
In twenty two (8,8%) patients both virus and bacterial have been isolated.
Patients with bacterial growth presented plasma CRP (C reactive protein) levels in 55% (using a cutoff of 12 mg/l), and of sputum IL-8 (median 715 pg/ml, v.s. 278 pg/ml, p=0,001).
Patients with viral growth presented plasma CRP in 25% and of sputum IL-6 (median 95 pg/ml v.s.6.3 pg/ml, p=0,01).
Conclusion: In COPD exacerbation microbiological aethyology had higher inflamatory response (sputum IL-8, CRP) and pulmonary function impairment, than viral evidence.

E308

Serum uric acid levels among patients with COPD exacerbations

Zorica M. Lazic, Vojislav B. Cupurdija, Ljiljana A. Novkovic, Cekerevac V. Ivan, Olgica M. Gajovic. *Pulmonary Department, Clinical Center Kragujevac, Kragujevac, Serbia, Serbia & Montenegro*

The aim of this study was to determine relationship between serum uric acid levels and severity of airway limitation in patients with acute exacerbations of COPD.

Method: We analyzed 48 hospital admitted patients with clinical sign of acute exacerbations of COPD. Simultaneous blood extraction for serum uric acid (SUA) and ABG were determined. Spirometry was performed in all patients. According to the severity of obstruction patients were divided into three groups: group I FEV 1 > 50% (11 pts, SUA 517, 86 ± 168,75), group II FEV1 30-50% (32pts, SUA 516,47 ± 127,01), group III FEV 1< 30% (14pts, 395,64 ± 144,65) predicted value. According to the serum uric acid level patients were divided into two groups: group I with normal SUA (< 430 μmol/l); group II with elevated SUA (>430 μmol/l). We analyzed relationship between lung function, PaO2, PaCO2 with serum uric acid level. Correlation analyses were used to determine association of different variables. To determine relationship between uric acid with ABG and severity of airflow limitations we were used independent t-test and ANOVA.
Results: Serum acid level was the highest in the very severy COPD patients. In the group patients with elevated AUA we find severe airflow limitations, (FEV1 38,04 ± 17,31%), hypoxemia (Pa O2 7,43 ± 1,90 kPa) and hypercapnia (PaCO2 -7,53 ± 2,25 kPa). A high significant correlation was noted between hipercapnia and serum uric acid level in acute exacerbation of COPD.
Conclusion: Serum acid level could be o good indicator for COPD severity and hipercapnia in patients with acute exacerbation of COPD.

E309
Prevalance of deep-vein thrombosis of the leg in acute exacerbations of COPD
Gulcin Pala, Murat Kiyik, Huseyin C. Tigin, Ebru Artan, Tunc Karadeli, Selim Intepe, Begum Kocak, Hayati Ozyurt, Sadettin Cikrikcioglu. *Pulmonary Diseases, Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital, Istanbul, Turkey*

Introduction: Major cause of acute exacerbations of COPD is infections. Heart failure, pulmonary embolism, pneumothorax, respiratory depressant drugs and some metabolic disorders are other reasons. Acute exacerbation of COPD is characterized by dyspnea and reduced mobility. Reduced mobility is a recognized risk factor for deep-vein thrombosis. So that we have investigated deep- vein thrombosis prevalance in patients with acute exacerbation of COPD prospectively.
Materials and methods: We prospectively included in the study 36 patients who had been hospitalized for an acute exacerbation of COPD according to ATS (American Thoracic Society) and ERS (European Respiratory Society)criteria between january 2004 and February 2006. We classified patients according to lung function tests on the base of GOLD classification.hemogram, lung function tests, d-dimer test and bilateral lower extremity venous doppler usg performed in all patients.
Results: Mean age of the patients was 64.22±10.52 and 3.3% of patients were satge 1(1 patient), 36.7% stage 2(11 patients), 64% stage 3 (18 patients) according to COPD staging.D-dimer test was in normal range in 83.3% of patients and high in 16.7% of patients.Deep-vein thrombosis was determined in two patients (5.6%) D-dimer test was high in 1 patient and negative in 1 patient who had deep-vein thrombosis.

E310
The character of COPD exacerbation
Gusein V. Ashyrov, Julia A. Mikryukova, Galina L. Ignatova, Elena V. Blinova, Lyudmila M. Chusova. *Therapy and Phthysiopulmonology, Ural State Medical Academy Posdyploma Education, Chelyabinsk, Russia*

The aim was to estimate the character of exacerbation of COPD by researching the cytologic character of expectorating sputum in this patients. Materials were over 80 men are included in the present research with diagnosis COPD at risk and COPD I-III stages in the age of from 40 till 60 years. All patients were surveyed in dynamics: during an exacerbation and remission of disease. The workers of a tractor plant had mainly mucous and mucopurulent character of sputum, as against group of the patients who are not working at the enterprise where purulent character of sputum prevailed, during an aggravation of illness. Statistically authentic distinctions have been received also between groups COPD at risk and COPD I-III from the persons living in area of the large industrial enterprise, but not working on it. So, purulent sputum was authentically more often symptom of chronic bronchitis, than in COPD I-III at these patients.
Conclusion: In our opinion, the aggravation of disease at the persons living in area of a factory, was caused by the infectious reasons is more often, and at patient - working at a factory a paramount trigger role contact to production factors of inflammation could play actions.

E311
The TORCH (TOwards a Revolution in COPD Health) study: salmeterol/ fluticasone propionate (SFC) improves survival in COPD over three years
Peter M.A. Calverley[1], Bartolome Celli[2], Julie A. Anderson[3], Gary T. Ferguson[4], Christine Jenkins[5], Paul W. Jones[6], Jørgen Vestbo[7], Julie C. Yates[8], Neil Pride[9]. *[1]University Hospital, Liverpool, UK; [2]GlaxoSmithKline R&D, Greenford, UK; [3]St. Elizabeth's Medical Centre, Boston, MA, USA; [4]Pulmonary Research Institute of Southeast Michigan, Livonia, MI, USA; [5]Woolcock Institute of Medical Research, Sydney, Australia; [6]St. George's University of London, London, UK; [7]Wythenshawe Hospital, Manchester, UK; [8]GlaxoSmithKline R&D, Research Triangle Park, USA; [9]National Heart & Lung Institute, London, UK*

COPD is a major cause of morbidity and mortality worldwide, which is predicted to increase. 6112 patients (<60% predicted FEV_1, mean age 65yrs, 76% males, 44% predicted post-bronchodilator FEV_1; 3.7% reversibility to salbutamol as % of predicted, 43% current smokers) were randomised to receive salmeterol (SAL) 50μg (n=1521), fluticasone propionate (FP) 500μg (1534), SFC 500/50 (1533), or placebo (PL) (1524) bd in a 3 year double-blind study. The primary analysis was log-rank of time to all-cause mortality (SFC vs PL) at 156 weeks, adjusted for 2 interim analyses which were carried out by an independent data monitoring board. SFC reduced the risk of dying at any time in the three years by 17.5% vs PL (p=0.052) (absolute rates 15.2% vs 12.6%).

Analysis	Hazard Ratio	95% CI	P value
Log rank unadjusted	0.820	0.677-0.993	0.041*
Log rank adj for 2 interim analyses	0.825	0.681-1.002	0.052
Cox's proportional hazards	0.811	0.670-0.982	0.031

*compared to p-value of 0.04.

SAL and FP were not significantly different to PL (SAL HR 0.879, 95% CI 0.729-1.061; FP HR 1.060, 95% CI 0.886-1.268). No significant interactions by baseline FEV_1 (<30%, 30-50%, >=50%), smoking, age or sex were found (all p>=0.12). SFC is the first intervention since O_2 and smoking cessation to improve survival in COPD.

E312
The TORCH (TOwards a Revolution in COPD Health) study: salmeterol/ fluticasone propionate (SFC) improves health status, reduces exacerbations and improves lung function over three years
Bartolome Celli[1], Peter M.A. Calverley[2], Julie A. Anderson[3], Gary T. Ferguson[4], Christine Jenkins[5], Paul W. Jones[6], Jørgen Vestbo[7], Julie C. Yates[8], Neil Pride[9]. *on behalf of the TORCH investigators; [1]St. Elizabeth's Medical Centre, Boston, MA, USA; [2]University Hospital, Liverpool, UK; [3]GlaxoSmithKline R&D, Greenford, UK; [4]Pulmonary Research Institute of Southeast Michigan, Livonia, MI, USA; [5]Woolcock Institute of Medical Research, Sydney, Australia; [6]St. George's University of London, London, UK; [7]Wythenshawe Hospital, Manchester, UK and Hvidovre Hospital, Denmark; [8]GlaxoSmithKline R&D, Research Triangle Park, USA; [9]National Heart & Lung Institute, London, UK*

COPD is linked to premature death and is associated with progressively worse health status, increased exacerbations and lung function limitation. TORCH was a 3 year, double-blind, placebo controlled multi-centre trial of 6112 (ITT population) patients with COPD (mean age 65 yrs, 76% males, 44% predicted post-bronchodilator FEV_1, 43% current smokers, 3.7% reversibility to salbutamol). Patients received salmeterol (SAL) 50μg (n=1521), fluticasone propionate (FP) 500μg (1534), SFC 500/50 (1533), or placebo (PL) (1524) bd. Health status (St George's Respiratory Questionnaire) and moderate/severe exacerbations were secondary outcomes. Post-bronchodilator FEV_1 was also assessed in the study.

Table 1. Treatment difference

	SFC vs PL (95% CI)	SFC vs SAL (95% CI)	SFC vs FP (95% CI)
SGRQ Total score (units)	-3.1 (-4.1, -2.1) p<0.001	-2.2 (-3.1, -1.2) p<0.001	-1.2 (-2.1, -0.2) p=0.017
Moderate/severe * exacerbations rate ratio	0.75 (0.69, 0.81) p<0.001	0.88 (0.81, 0.95) p=0.002	0.91 (0.84,0.99) p=0.024
Postbronchodilator FEV_1 (mL)	92 (75,108) p<0.001)	50 (34,67) p<0.001	44 (28,61) p<0.001

*moderate: antibiotics and/or systemic corticosteroids; severe: hospitalisation.

The mortality benefit with SFC vs PL reported elsewhere is supported by significant improvements in three pillars of clinical management of COPD: improvement in health status and lung function, and reduction in exacerbations. SFC was superior to PL and components for all three efficacy outcomes. These findings have important implications for patients, clinical practice and healthcare systems.

E313
The TORCH (TOwards a Revolution in COPD Health) study: salmeterol/ fluticasone propionate (SFC) is well tolerated in patients with COPD over three years
Gary T. Ferguson[1], Peter M.A. Calverley[2], Julie A. Anderson[3], Bartolome Celli[4], Christine Jenkins[5], Paul W. Jones[6], Jørgen Vestbo[7], Julie C. Yates[8], Neil Pride[9]. *On behalf of the TORCH investigators; [1]Pulmonary Research Institute of Southeast Michigan, Livonia, MI, USA; [2]University Hospital, Liverpool, UK; [3]GlaxoSmithKline R&D, Greenford, UK; [4]St. Elizabeth's Medical Centre, Boston, MA, USA; [5]Woolcock Institute of Medical Research, Sydney, Australia; [6]St. George's University of London, London, UK; [7]Wythenshawe Hospital, Manchester, UK and Hvidovre Hospital, Denmark; [8]GlaxoSmithKline R&D, Research Triangle Park, USA; [9]National Heart & Lung Institute, London, UK*

The safety profile of SFC and components was assessed in the three year TORCH study. The safety population was 6184 COPD patients (mean age 65yrs, 76% males, 44% mean predicted post-bronchodilator FEV_1; 3.7% reversibility to salbutamol; 43% current smokers) who received salmeterol (SAL) 50μg (n=1542); fluticasone propionate (FP) 500μg (1552), SFC 500/50 (1546) or placebo (PL) (1544) bd. Total treatment years exposure was 3531 (SAL), 3555 (FP), 3700 (SFC) and 3278 (PL). Overall incidence of investigator reported adverse events (rate per treatment year)