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# Montelukast therapy and psychological distress in chronic obstructive pulmonary disease (COPD): A preliminary report

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is an alteration in which ventilatory function, exercise capacity and health status of patients progressively decline and it is characterized by an increase of inflammatory cytokines such as TNF-α, LTB4, IL-8, etc. In this study we considered twenty patients (15 males and 5 females; mean age: 72.8 ± 6.3) with stable COPD. All patients were performed evaluation of psychological stress at enrollment and were treated with leukotriene receptor antagonists (montelukast tablets) 10 mg/day for 12 months. After 12 months we observed a significant decrease of serum levels of LTB4, IL-8 and also a decrease of the number of outpatient clinic visits, of the number of hospitalizations and of the duration of hospitalization.



## 1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are very common inflammatory diseases of the airways. They both cause airway narrowing and are increasing in incidence throughout the world, imposing enormous burdens on health care COPD is a leading course of morbidity and mortality in which ventilatory function, exercise capacity and health status of patients progressively decline and exacerbations of symptoms may affect them with varying frequency (White et al., 2003; Angerio, 2008). Airway inflammation is a key feature in COPD, resulting in mucus hypersecretion, airway narrowing, alveolar destruction and higher sputum concentration of inflammatory molecules. Cytokines play a key role in orchestrating the chronic inflammation and structural changes of the respiratory tract in both asthma and COPD and have become important targets for the development of new therapeutic strategies in these diseases (Stevens et al., 1992; Bhowmik et al., 2000; White et al., 2003; Barnes, 2008). Inflammatory mediators, mostly released by neutrophils infiltrating lung tissue, play a central role in the pathogenesis of the tissue damages, with subsequent evolution to fibrosis. Chemoattractants, particularly interleukin (IL)-8 and leukotriene LTB4, recruit neutrophils in lung tissue via adhesion molecules expressed on vascular endothelium (Chang, 1994; White et al., 2003). Neutrophils release various mediators responsible for the pathogenesis of lung damage and of acute exacerbations (Hiemstra et al., 1998; White et al., 2003).

Patients with more frequent relapses per year have higher sputum concentration of IL-6 and IL-8, whereas TNF-α contributes to the increases of IL-8 production (Cromwell et al., 1992; Bhowmik et al., 2000). Moreover, several inflammatory diseases, including asthma, chronic obstructive pulmonary disease, arthritis and inflammatory bowel disease, have been associated with elevated levels of LTB4 (Hicks et al., 2007). Cysteinyl leukotrienes increase microvascular permeability, evoke mucus hypersecretion and elicit airway smooth muscle contraction, and some of these features are also present in patients with COPD (McMillan, 2001; Rubinstein et al., 2004; Laurin et al., 2007). Montelukast is a cysteinyl leukotriene receptor antagonist (LTRA) designed to inhibit the interaction between cysteinyl leukotrienes and their receptors on effector cells (Schmitt-Grehe and Zielen, 2005). In the light of these immunologic mechanisms, it has been proposed that leukotriene receptor antagonists might be useful in the long-term management of COPD (Riccioni et al., 2004; Rubinstein et al., 2004; Hicks et al., 2007; Laurin et al., 2007).

COPD is a disease that is not confined to the airways and the lungs, but also produces systemic consequences as well as the systemic inflammation and the inactivity (Decramer, 2008). Rehabilitation is the best treatment for muscle weakness and deconditioning in patients with COPD and which with the largest effect on health status and exercise capacity in these patients. Several factors that may enhance the effects of rehabilitation have been studied. These include: growth hormone/IGF-I, anabolic

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steroids, anti-cytokine treatment, erythropoietin, oxygen, non-invasive mechanical ventilation and electrical stimulation (Decramer, 2008).

Increasing body of evidence indicates a link between psychological stress and chronic inflammation (Elenkov et al., 2005; Glaser, 2005). Stressful life events appear to contribute to asthma's exacerbations in subjects with existing illnesses (Singer et al., 2001; Liu et al., 2002; Sandberg et al., 2004; Wright et al., 2005). Psychological stress may also affect response to therapies (Ippoliti et al., 2006). In addition, among elderly people affected by COPD, psychological distress might be a predictor of health adverse events (Andenaes and Kalfoss, 2004).

Negative impacts of depression and anxiety have been established for chronic diseases such as coronary artery disease, diabetes mellitus, and hypertension (Hiemstra et al., 1998; Gruffydd-Jones et al., 2007), but poorly studied in COPD. As a matter of fact, a possible association between depression and exacerbations, as well as hospitalizations in stable COPD have only been described quite recently (Xu et al., 2008). Anxiety about breathlessness affects the sleep experience of patients with COPD, and sleep quality impacts on physical and emotional functioning (Shackell et al., 2007).

Measurements of pulmonary biomarkers can be used to monitor airway inflammation in COPD, but the variability of sampled biomarkers and their inter-relationships are poorly understood. A study was undertaken to examine the intra- and inter-patient variability in spontaneous sputum samples from patients in the stable state and to describe the relationship between biomarkers, cell counts and markers of disease (IL-1β, TNF-α, IL-8, myeloperoxidase, LTB4, growth-related oncogene-α). There was significant variability in all inflammatory indices (Sapey et al., 2008).

We hypothesize that these findings can be due also to individual psychological stress. For this reason the main objective of this study was to evaluate the efficacy of a 12-month course of montelukast treatment in elderly patients affected by stable COPD, divided in two groups based on the perceived stress.

Clinical characteristics and serum concentration of inflammatory cytokines were compared between the two groups, to evaluate if there was any possible relationship with psychological stress, together with the higher level of IL-8 and LTB4, to underline the role of the distress as a risk factor for maintenance and progression of the disease. In fact, many authors describe that interventions reducing relapses for COPD need to be considered as the psychosocial as well as the medical needs of patients (Andenaes and Kalfoss, 2004; Chetta et al., 2005; Pembroke et al., 2006; Gruffydd-Jones et al., 2007; Decramer, 2008).

## 2. Patients and methods

In our study we enrolled 20 patients (16 males and 4 females; mean age: 72.8 ± 6.3) with stable COPD, periodically observed in our ambulatory. The diagnosis of COPD was based on clinical history, symptom assessment, X-ray and computed tomography (CT) evaluation, and pulmonary function test (PFTs) assessments.

Patients were eligible if they met the inclusion criteria (diagnosis of stable COPD with mild chronic respiratory deficit and absence of COPD-related diseases). All patients were in absence of acute exacerbations for at least 6 months. Exclusion criteria were the presence of acute exacerbations, the presence of asthma or any other concomitant inflammatory lung disease, the presence of inflammatory or autoimmune or neoplastic diseases, the need of inhaled or systemic steroid treatment during the 3 months preceding the enrollment and an active smoking status during the 12 months preceding the enrollment.

All patients were treated with the LTRA (montelukast) 10 mg/day for 12 months. The aim of these treatments was to describe the long-term effect of montelukast therapy. Patients were not allowed to take steroid therapy during the study, but they were allowed to take inhaled 2-agonists or oral teofillins if needed.

At the moment of diagnosis (T0) a complete history was collected. In particular, we assessed the severity and frequency of dyspnoea, the presence of copious production of sputum, the use of oral teofillins, inhaled 2-agonists and $O_2$-therapy, the frequency of emergency department (ED) visits due to acute exacerbations, the number and length of disease-related hospitalizations. The same data were collected during the 12-month study period (T1) by means of diary cards and physician's assessment. PFTs were performed at T0 and after 12 months of treatment, at the end of the study (T1), FEV1 was assessed and compared with their predicted values (based on age, sex, height, weight, smoking status).

Evaluation of psychological stress was performed at T0 using the Italian version of the Mèsure du Stress Psychologique for perceived stress (Di Nuovo et al., 2000; Lemyre and Tessier, 2003). This test involves a 49-item questionnaire based on different perceived aspects regarding the patient's state (cognitive, physiological and behavioral aspects); the patient indicates intensity for each item on a scale of 1–4 and the values are then added to give the total score. Convergence validity was established with classical depressive and anxiety scales (Lemyre and Tessier, 2003). The obtained stress integrated measure (SIM) values express a functional configuration for each patient on a scale of 0–100, with 100 indicating maximum perceived stress. A cut-off value of 30 was used to divide patients with low level of perceived stress (SIM $< 30$) versus patients with high level of perceived stress (SIM $> 30$) groups (Lemyre and Tessier, 2003; Ippoliti et al., 2006).

Blood was drawn from fasting patients at the same time (8.30 a.m.) to avoid physiological circadian variations. Serum concentrations of human IL-12 p70, TNF-α and IL-8 were measured by means of ELISA assays (R&D Systems, Minneapolis, MN, USA, detection limit 5, 1.6, and 3.5 pg/ml, respectively). Serum concentration of IL-6 was assessed by ELISA assay (Immunological Sciences, detection limit 0.5 pg/ml). Serum concentration of LTB4 was assessed by means of EIA assay (Assay Designs, Inc., Technology Drive, Ann Arbor, Miami, detection limit 5.63 pg/ml).

Due to the small sample size, all the data were evaluated for statistical significance by means of nonparametric tests. Within-group analysis was performed by mean of the Wilcoxon's test, while Mann–Whitney test was used for between-group comparisons. Pearson's $\chi^2$-test was used for the comparison of nominal variables. Bonferroni's correction was used for multiple analyses. Statistical significance was attributed to $p < 0.05$. All statistical analyses were performed using the StatView software, version 5.0 (SAS Institute, Inc., Cary, NC, USA). All data are expressed as mean ± S.D.

## 3. Results

The clinical characteristics of the studied subjects before treatment (T0) and after 12 months of montelukast therapy (T1) are summarized in Table 1. The presence of dyspnoea, copious production of sputum and bronchospasm, the need of inhaled 2-agonists or oral teofillins, the number of visits, the number of patients needing hospitalization and its length were significantly improved after montelukast therapy; on the contrary, PFT assessment did not show any significant difference after therapy.

Regarding the stress evaluation, 15 patients showed a level of perceived stress $> 30$ (mean value of SIM 70.4 ± 15.6) and only 5 had perceived stress $< 30$ (mean value of SIM 22.4 ± 13.5). No significant differences between the two groups were observed in clinical characteristics (data not shown).

**Table 1**
The clinical characteristics of the studied subjects before treatment (T0) and after 12 months of montelukast therapy (T1), % or *n*.

| 20 patients (age 72.8 ± 6.3) | T0 | T1 |
|---|---|---|
| Dyspnoea | 90 | 40 |
| Sputum | 70 | 30 |
| Bronchospasm | 55 | 25 |
| FEV1 | 79.5 ± 32.4 | 75.0 ± 25.1 |
| Patients who need of inhaled 2-agonists | 100 | 75 |
| Patients who need oxygen-therapy | 30 | 20 |
| Mean outpatient clinic visits per year | 3.7 | 2.2 |
| Mean number of hospitalization per year | 3.1 | 1.4 |
| Mean length of hospitalization (days per year) | 6.8 | 3.6 |

Before treatment, the serum concentration of LTB4 in all enrolled patients was 3958 ± 3422 pg/ml, but it was significantly higher among patients with stress. After 12 months of treatment, LTB4 concentration of the whole study group decreased to 2292 ± 1732 pg/ml, and it was significantly decreased in patients with SIM > 30 (Fig. 1). Similarly, before treatment TNF-α concentration was 9.9 ± 26.9 pg/ml in all studied patients, significantly higher among patients with stress; after therapy, TNF-α decreased to 3.7 ± 6.0 pg/ml, with significant decrease only among the same group (Fig. 2).

At T0 the mean of IL-8 level in all studied patients was 18.9 ± 11.4 pg/ml, and it was significantly higher in patients with stress. After treatment, IL-8 concentration decreased to 10.2 ± 5.2 pg/ml, but, similarly to LTB4 and TNF-α, this decrease was almost entirely due to the patients with high stress levels (Fig. 3).

On the contrary, the concentration of IL-6 and IL-12p70 was not significantly different between the two groups at both times (data not shown).

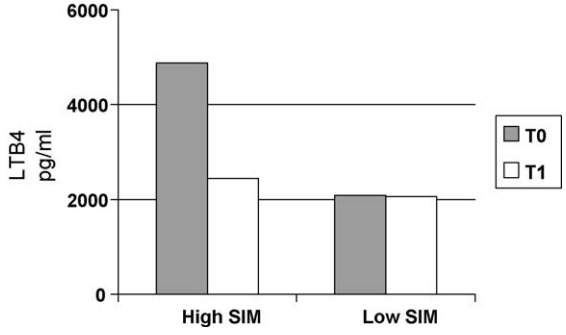


**Fig. 1.** Serum concentration of LTB4 in the studied subjects. At T0, LTB4 concentration was 5570 ± 3167 pg/ml in high SIM patients (*n* = 15) and 2643 ± 1779 pg/ml in low SIM patients (*n* = 5). At T1, LTB4 concentration was 2367 ± 1572 and 2066 ± 2127 pg/ml, respectively.

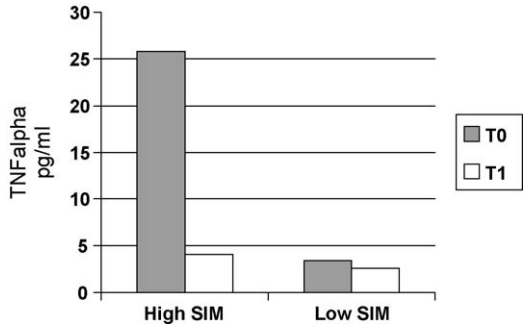


**Fig. 2.** Serum concentrations of TNF-α. At T0, TNF-α concentration was 25.8 ± 27.3 pg/ml in high SIM patients (*n* = 15) and 3.4 ± 1.5 pg/ml in low SIM patients (*n* = 5). At T1, TNF-α concentration was 4.1 ± 6.7 and 2.6 ± 3.2 pg/ml, respectively.

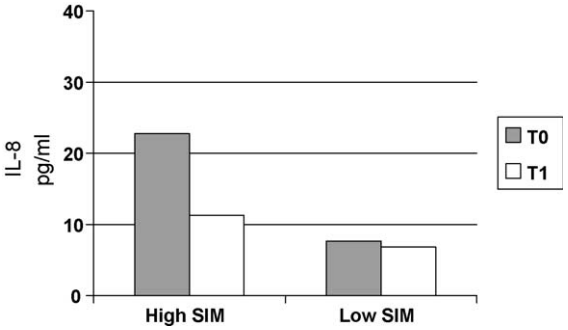


**Fig. 3.** Serum concentration of IL-8 among the two groups. At T0, IL-8 concentration was 22.7 ± 10.6 pg/ml in high SIM patients (*n* = 15) and 7.6 ± 2.9 pg/ml in low SIM patients (*n* = 5). At T1, IL-8 concentration was 11.3 ± 5.2 and 6.8 ± 3.2 pg/ml, respectively.

## 4. Discussion

Psychological distress has been shown to be a predictor of adverse health effects in medically ill elderly people, including COPD patients (Andenaes and Kalfoss, 2004; Elenkov et al., 2005; Laurin et al., 2007). In addition, psychological stress can also promote inflammatory responses through effects on sympathetic and parasympathetic nervous system pathways. Recent evidences indicate that stress hormones induce systemically a Th2 shift, however in certain local responses they may induce pro-inflammatory activities (Elenkov et al., 2005). Exposure of animals to mild inescapable electrical food shock stress results in increased production of IL-1b and TNF-α by alveolar macrophages and lung mononuclear cells. In addition stress hormones increase the production of IL-8, thus promoting, together with LTB4, the recruitment of inflammatory cells in the lung. Also activated neutrophils release IL-8 and LTB4 that could contribute to the pathogenesis of chronic inflammatory lung diseases (Matsuzaki et al., 2006). We can suppose that montelukast therapy reduces systemic pro-inflammatory cytokines stress-related by Th2 shift: in fact IL-6 and IL-12 were in the normal range.

In turn, pro-inflammatory cytokines interact with many of the pathophysiological domains that characterize depression, such as neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and behavior (Raison et al., 2006; McEwen, 2008). Psychiatric disorders are at least three times higher in COPD patients compared to the general population (Laurin et al., 2007). Our findings further support the view that stress may contribute to inflammation in local responses, such as in the lung. In fact, our results that LTB4, IL-8 and TNF-α concentration is significantly higher among patients with stress at baseline and decrease after treatment might confirm that psychological distress may play a role in the pathogenesis of the status of chronic inflammation seen in patients with stable COPD, unlike other studies in where the psychological stress is associated with unstable COPD.

We observed, after long-term montelukast therapy, a decreased serum concentration of LTB4, IL-8 and TNF-α that accompanies the reduction of dyspnoea, sputum and a significant decrease of the number of outpatient clinic visits, of the number of hospitalizations and of the duration of hospitalization, in agreement with the results of Rubinstein et al. (2004).

On the contrary, in our study the PFT assessment results not significantly different after 12 months of treatment, confirming, in an objective manner, that all the evaluated patients were in a stable clinical status, with a steady reduced lung function; the long mean duration of the disease, over 10 years, implies that the lung damage has been established and it can not be reduced with the use of drug therapy.

All these data seem to indicate that the symptom amelioration may be due to a reduction of the systemic chronic inflammation "stress-depending" (Goebel et al., 2000; Raison et al., 2006; McEwen, 2008). Obviously, the established tissue damage, particularly fibrosis, cannot be reverted by inflammation decrease, thus PFT assessment did not show any significant difference after therapy.

Finally, this study suggests that in patients with COPD the evaluation of psychological distress and of stressful events should be considered as relevant as the physical assessment. LTRA compounds, such as montelukast, may be a better non-steroid anti-inflammatory drug for stable COPD in preventing airway inflammation caused by cytokines in presence of psychological stress (Goebel et al., 2000; Itoh et al., 2003; Joppa et al., 2006; Gronke et al., 2008).

## Conflict of interest statement

None.

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