Personalised pharmacological therapy of chronic obstructive pulmonary disease based on inflammatory phenotyping

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Anti-inflammatory effect and efficacy of inhaled corticosteroids (ICS) in patients with stable chronic obstructive pulmonary disease (COPD) are variable. Cellular analysis of induced sputum is a non-invasive and standardised technique for direct assessment of airway inflammation (1). We hypothesised a selective anti-inflammatory effect of ICS in COPD patients with eosinophilic phenotype (sputum eosinophil counts>3%) as compared with those without sputum eosinophilia. We undertook a parallel group, open-label, pilot study in COPD patients (GOLD I-III) who were treated either with inhaled tiotropium (18 micrograms once daily) (group A) or inhaled tiotropium+fluticasone (500 micrograms b.i.d.) (group B). Study included a screening visit, a pre-treatment visit after one week run-in phase and a post-treatment visit after 4 week pharmacological treatment. Primary objective was assessing ICS effect on sputum eosinophils in patients with eosinophilic vs non-eosinophilic phenotype. Secondary objectives were assessing ICS effects on exhaled nitric oxide (FENO), a non-invasive marker of airway inflammation (2), urinary 15-F_{2t}-isoprostane (15-F_{2t}-IsoP), a marker of oxidative stress, and lung function. Fifteen COPD patients per group were required considering pre-treatment sputum eosinophil cell counts of 6.3±4% in patients with eosinophilic phenotype (3), a prevalence of eosinophilic phenotype of 38% in COPD population (3), that fluticasone can reduce sputum eosinophils to non-eosinophilic phenotype values (0.9±1.4%) (3), a power of 80%, alpha=0.05, a dropout rate and/or failure to obtain suitable sputum samples of 20%. Sputum induction and analysis were performed based on ERS guidelines (1). FENO was measured with a NIOX MINO (Aerocrine, Solna, Sweden) based on ATS/ERS guidelines (2). Urinary 15-F2t-IsoP was mesured with previously validated EIA (4). Fifteen patients per group were recruited. Twelve patients in group A [9/3, male/female, age 67±3 years, mean±SEM, 38 (23-57) pack-years, median and interquartile range, FEV_1 67.9±5.9% pred; eosinophilic phenotype (group A1), n=4; non-eosinophilic phenotype (group A2), n=8] and 12 patients in group B [10/2, male/female, age 68±2 years, 38 (31-59) pack-years, FEV_1 68.8±3.5% pred; eosinophilic phenotype (group B1), n=4; non-eosinophilic phenotype (group B2), n=8] provided suitable sputum samples. Compared with pre-treatment values [18.5 (3.6-43.5)% cell counts], tiotropium+fluticasone reduced sputum eosinophils in group B1 [1.5 (0.3-2.8)% cell counts, P=0.0046], but not in group B2 (P=0.15), to values similar to those observed in B2 at pre-treatment visit (P=0.22). Post-treatment sputum eosinophils were lower in group B1 than in group A1 (P=0.029). Treatment with tiotropium+fluticasone had no effect on other sputum cell types, improved pre-bronchodilator FEV_1 in both B1 (P=0.049) and B2 (P=0.023) group and reduced FENO concentrations in group B2 (P=0.038). Tiotropium alone had no effect on sputum cells, whereas improved pre-bronchodilator FEV_1 in group A2 (P=0.005), but not A1. In group A2, FENO was increased after tiotropium alone (P=0.01). Both pharmacological treatments had no effect on urinary 15-F_{2t}-IsoP.

Inhaled fluticasone selectively reduces airway inflammation in COPD patients with eosinophilic phenotype, but not in those with non-eosinophilic phenotype. In patients with sputum eosinophilia, tiotropium+fluticasone improves FEV_1, an effect which is not observed with bronchodilator alone. Long-term large prospective controlled studies are required for establishing the implications of these effects for reducing exacerbation rate and/or lung function decline in COPD patients with eosinophilic phenotype.

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