# 489. Clinical diagnosis and treatment of adult asthma

**4692**

**A proof-of-concept randomized-controlled trial of omalizumab in patients with severe difficult to control nonatopic asthma**

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While up to 50% of severe asthma patients have no evidence of allergy, IgE has been linked to asthma in epidemiological and immunopathological studies, irrespective of atopic status. Omalizumab (OMA), an anti-IgE monoclonal antibody, is reported to significantly benefit a subset of patients with poorly controlled severe persistent allergic asthma. Therefore biological and clinical effects of OMA were investigated in patients with refractory nonatopic asthma.
**Methods:** 41 patients with severe nonatopic asthma uncontrolled despite daily high-dose inhaled corticosteroids (with or without maintenance oral corticosteroids) plus a long-acting $\beta_2$-agonist were randomized to receive OMA or placebo in a 1:1 ratio. Primary end-point was change in expression of high-affinity IgE receptor FcεRI on blood basophils and plasmacytoid dendritic cells (pDC2) after 16 weeks. The impact on lung function and clinical parameters was also assessed.
**Results:** When compared to placebo, OMA treatment resulted in a statistically significant reduction in FcεRI expression on blood basophils and pDC2 ($p<0.001$). The OMA group also showed an overall increase in placebo-adjusted predicted $FEV_1$ compared to baseline (+9.9%; p=0.029). The placebo-adjusted absolute change in $FEV_1$ with OMA was +250 ml (p=0.032). A trend toward improvement in global evaluation of treatment effectiveness scale and asthma exacerbations rate was also observed.
**Conclusion:** Omalizumab treatment may have a therapeutic role in severe nonatopic asthma. These findings support further investigation to assess the clinical efficacy of omalizumab in severe persistent nonatopic asthma.
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**Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control**

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Evolution of severe asthma after discontinuation of omalizumab (OMA) (Xolair®) for good asthma control is still not very well known. This study provides real-life data in this situation.
**Methods:** Observational, descriptive, cross-sectional, retrospective study in which 24 pulmonologists recorded data on patient and asthma characteristics during OMA treatment prescribed in patients with severe persistent allergic asthma uncontrolled despite best available therapies, and after OMA discontinuation (minimal follow up required = 6 months), for all their patients in who OMA had been discontinued due to achievement of good asthma control.
**Results:** Data from 61 patients were collected [characteristics at OMA initiation: females 65.6%; mean age 40.7 yrs (min 6, max 82); mean asthma duration 22.3 yrs]. Mean duration of OMA treatment was 22.7 months ($CI_{95\%}$: 19.4-26.0). Mean duration of good asthma control before discontinuation was 11.8 months ($CI_{95\%}$: 12.0-18.1). Mean change in $FEV_1$ under OMA was +13%. After OMA discontinuation, median follow up duration was 9.26 months, loss of control was observed in 34 patients (55.7%) for who median time to loss of control was 13 months ($CI_{95\%}$: 8.2-28.1). The % of patients with an observed loss of control were 69.2%, 59.1% & 45.7% after respectively <1 year, 1-2 years & >2 years of OMA treatment. OMA was reintroduced in 20 out of the 34 patients with loss of control: 14 were responders (70%), 4 not responders (20%) & 2 not yet evaluable (10%).
**Conclusion:** Proportion of observed loss of control depended on prior treatment duration. Most of patients were still responders after OMA reintroduction.
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**Rhinovirus infection activates coagulation through eosinophilic airway inflammation**

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**Introduction:** Exacerbations in asthma are most commonly caused by rhinoviruses. Inflammatory conditions, like asthma, are known to activate hemostasis. *Vice versa*, a prothrombotic state in the lung can also induce or aggravate pulmonary inflammation.
**Hypothesis:** Rhinovirus infection activates coagulation in patients with asthma, but not in normal control subjects.
**Methods:** 14 patients with mild asthma and 14 healthy controls were nasally inoculated with rhinovirus type 16 (10 $TCID_{50}$) using a validated method. Bronchoalveolar lavage fluid (BALF) was retrieved by bronchoscopy at t=-1 and t=6 days. Microparticle-associated tissue factor(TF) activity in BALF was examined by a fibrin generation test (FGT). Thrombin-antithrombin complexes (TAT) and Eosinophil Cationic Protein (ECP) in BALF were measured by immunoassay. Eosinophils were counted on cytospin preparations.
**Results:** On day 6 after rhinovirus infection, FGT in BALF became significantly shorter in asthma (t=-1: 672s vs. t=6: 516s (medians); p=0.013), whereas there was no change in healthy controls (t=-1: 695s vs. t=6: 707s (medians); p=0.75). At t=6 days, FGT correlated (Spearman) with TAT, eosinophils and ECP (r = -0.607, -0.583 and -0.682 resp., all $p<0.01$) and TAT with eosinophils and ECP (r = 0.482, 0.538, both $p<0.05$).
**Conclusion:** Rhinovirus infection significantly shortens the clotting time (FGT) when induced by microparticles isolated from BALF of asthma patients, reflecting enhanced coagulant activity of TF-exposing microparticles. The strong correlations between FGT, TAT, eosinophils and ECP after rhinovirus infection in asthma suggest that eosinophils may play a critical role in the coagulation activation during viral airway infection.

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**Exhaled air volatile organic compounds and eosinophilic airway inflammation in asthma**

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**Rationale:** Eosinophilic inflammation in asthma is predictive for responses to inhaled steroids. The application of sputum analysis is somewhat limited by requirement of lab facilities and not-directly available results. Exhaled air metabolomics is associated with eosinophilic inflammation in COPD (Fens *et al.* ERJ 2011). We hypothesized that breath volatile organic compounds (VOCs) can be adequate surrogate markers of airway inflammation in asthma.
**Aim:** To identify VOCs in exhaled air by gas chromatography and time-of-flight mass spectrometry (GC-TOFMS) that can discriminate eosinophilic asthma from non-eosinophilic asthma.
**Methods:** Breath samples were analysed by GC-TOFMS in 40 patients (>18yr) with moderate/severe asthma (GINA-criteria). All patients were non-smokers and required inhaled corticosteroids (≥500ug FP or equivalent). Differential cell counts were measured in induced sputum. Correlation coefficients and corresponding p-values between the peaks and measured sputum eosinophils were calculated by univariate analysis (p-value<0.01).
**Results:** Sputum was successful in 36 patients, of which 21 patients had sputum eosinophils >3%. Linear regression analysis showed associations for 5 VOCs with sputum eosinophils. The correlation coefficients varied between 0.42-0.47. When excluding patients on oral corticosteroids (n=8), 8 VOCs were associated with sputum eosinophils with higher correlation coefficients varying between 0.49-0.62.
**Conclusion:** Exhaled air VOCs are modestly associated with sputum eosinophils

in patients with moderate/severe asthma on (inhaled) steroids. This suggests that exhaled breath analysis requires further optimisation in the assessment and monitoring of airway inflammation in asthma.

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**IgE-autoantibodies and adipokines in patients with bronchial asthma and obesity**

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The adipose tissue represents an important source of inflammatory cytokines with pro-allergic activity. We *aimed* to estimate the influence of obesity on the characteristics of autoreactivity and cytokine repertoire in patients with bronchial asthma (BA) as compared to allergic rhinitis (AR) and healthy.
**Methods:** Body mass index (BMI) was evaluated in 80 patients with AR and BA and 25 healthy people. By ELISA were measured serum level of C reactive protein (CRP), IgE- autoAbs to keratin, collagen type III and elastin and production of TNF-α and IL-4 from blood lymphocytes.
**Results:** Atopic patients with BMI >30 kg/m(2) had elevated levels of CRP (744±28 ng/ml) and high spontaneous production of TNF-α (45±4 ng/ml) and IL-4 (9.5±2.8 ng/ml) in comparison with normal-weight patients and healthy (7.3±2.7 ng/ml, 3±0.6 ng/ml and 1.7±0.3 ng/ml accordingly). The group of obese asthmatics distinguished with highest levels of CRP (1560±28 ng/ml) and IgE-autoAbs to keratin and collagen III, which correlated with BMI (R=0,58) and were elevated in comparison with preobese and normal-weight patients with BA and AR. Serum leptin was overproduced in BA significantly among obese (57±7.1 ng/ml) via non-obese patients (23±6 ng/ml) and showed no difference between healthy subjects independently from BMI (6.1±0.3 ng/ml).
**Conclusions:** Asthmatics with BMI >30 kg/m(2) show a special phenotype of disease with elevated serum leptin and pro-inflammatory markers, which needs to be managed and treated distinctly. Obesity is attended with higher generation of IgE-autoAbs, which can indicate the disturbance of immune regulation.

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**Effect of bariatric surgery on asthma: 3 months follow-up**

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**Background:** Asthma in obese subjects is poorly understood and the effect of weight loss on asthma control is not well described.
**Aim:** To investigate the effects of bariatric surgery on asthma control, quality of life and lung function.
**Methods:** We performed a prospective study in patients with confirmed diagnosis asthma ($\Delta FEV_1 \geq 12\%$ or PD20<1.76mg(=BHR)) and non asthmatic patients undergoing bariatric surgery(BMI >35kg/m$^2$, age 18-50y). Lung function, medication and quality of life were assessed at baseline and 3 months after bariatric surgery. Obese asthmatics who did not undergo bariatric surgery served as an additional control group.
**Results:** 35 asthma patients(O+A) and 50 non-asthmatics(O-A) underwent bariatric surgery, 17 asthma patients served as controls(NO+A). There were no differences in ACQ, AQLQ, $FEV_1$ or FeNO between O+A and NO+A at baseline. BMI of NO+A(40kg/m$^2$) was significantly lower than O+A(47kg/m$^2$). After bariatric surgery, BMI decreased to 38kg/m$^2$ in O+A, and BHR decreased significantly in O+A(80% to 34%, p=0.003). In addition, use of ICS decreased with 50%. $FEV_1$ improved significantly only in O+A(mean 85.6 to 94.6%pred, p=0.011). Following surgery, ACQ and AQLQ significantly improved in O+A group(1.1 to 0.5, p=0.022; resp. 5.7 to 6.3 p=0.004), whereas no change was detectable after 3 months in NO+A. ACQ and AQLQ were significantly better in O+A group compared to NO+A after 3 months(ACQ p=0.027, AQLQ p=0.002). No change in FeNO in any group.
**Conclusion:** Bariatric surgery improves lung function, asthma control and quality of life in patients with asthma and morbid obesity already after 3 months. So it can be speculated that weight loss is an important component of the management of obese asthmatics.

**4698**

**Substitution of vitamin D in patients with moderate to severe persistent asthma: A randomized, placebo-controlled pilot study**

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**Background:** Vitamin $D_3$ stimulates glucocorticoid-induced IL-10 synthesis by regulatory T cells in patients with asthma. IL-10 is a potent antiinflammatory cytokine that can block asthmatic inflammation.
**Objective:** To study whether short-term calcitriol affects lung function and symptoms in patients with moderate to severe persistent asthma treated with a combination of long-acting beta-2-agonists and inhaled corticosteroids.
**Methods:** 20 outpatients (8m, 12f) with moderate to severe persistent asthma (mean age 58.4y, 36-83) were enrolled in this randomized, placebo-controlled, double-blind, double-dummy pilot trial with random crossover design. All were treated with a stable dose equivalent to ≥400 ug/day of budesonide and ≥12 ug/day of formoterol for at least 4 weeks. Patients were randomized to receive either calcitriol 1.0 μg once daily or placebo. Each treatment phase lasted for 4 weeks, interrupted by a 3-week treatment washout period. Treatment effect was calculated by subtracting baseline values from end of treatment values and using a linear mixed effects model to correct for period and sequence effect.
**Results:** Baseline FEV1 was 69.2%pred. (±11.9), 25-hydroxyvitamin D level 46.6 nmol/L (±21.8). FEV1%pred. increased by 1.4% (±7.5) during calcitriol compared to 0.2% (±5.5) during placebo treatment (p=0.64, n.s.). $FE_{NO}$, bronchial hyperreactivity, peak flow, asthma symptom scores and use of short-acting beta-2-agonists were also not significantly different between calcitriol and placebo periods.
**Conclusion:** Calcitriol did not improve lung function and asthma symptoms in this short term pilot study (ClinicalTrials.gov number, NCT 00712205).

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**BTS Difficult Asthma Registry: Effect of omalizumab dosing table expansion on size of population of severe persistent allergic asthma patients potentially eligible for omalizumab therapy**

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The dosing of omalizumab is determined by baseline serum total IgE and body weight. In 2010, the EU licence for omalizumab increased the maximum baseline total IgE in the dosing table from ≤700 IU/mL ('Standard' dose) to >700–1500 IU/mL ('Expanded' dose). Using data from the BTS Difficult Asthma Registry we evaluated the effect of this expansion on the size of the patient population with severe persistent allergic asthma potentially eligible for omalizumab therapy. 582 adult and adolescent patients were identified from all seven Specialist Centres that submit data to the Registry. Mean age was 21.4 (±18.6) years and mean IgE was 501 (±1546) IU/mL. With the expansion of the dosing table, the percentage increase in the pool of patients with severe persistent allergic asthma potentially eligible for omalizumab was less than 23%, when applying the omalizumab licence criteria (Population A). With the addition of the NICE criteria (Population B) an even smaller percentage increase in the patient pool was seen [Figure].

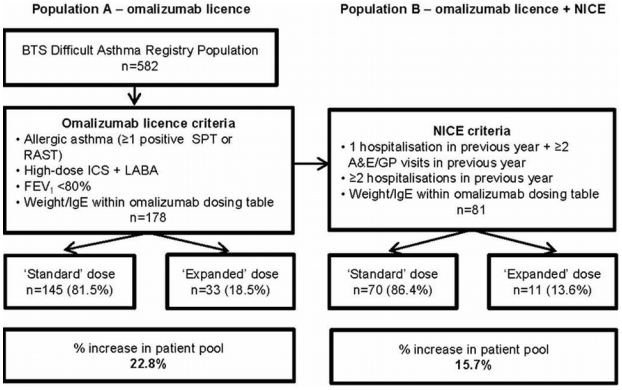


Figure 1. BTS = British Thoracic Society; SPT = skin-prick test; RAST = radioallergosorbent test; ICS = inhaled corticosteroid; LABA = long-acting $\beta_2$-agonist.

In conclusion, despite the expansion in license and application of NICE criteria, the change in the number of patients eligible for omalizumab treatment is relatively modest.