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Safety of bronchial thermoplasty out to 5 years in patients with severe refractory asthma: Research in severe asthma (RISA) trial

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Introduction: Bronchial thermoplasty (BT) is a bronchoscopic procedure designed to control asthma by reducing airway smooth muscle mass. BT-treated patients from the RISA Trial have been followed to evaluate long-term safety.
Methods: The RISA Trial enrolled 15 patients on ICS $\geq$1500μg BDP or equiv. + LABA $\pm$ $\leq$ 30mg OCS; pre-BD FEV_1 $\geq$50% predicted; and remained symptomatic (daytime symptoms on $\geq$10 of 14 days or rescue medication use on $\geq$8 of 14 days prior to enrollment). Long-term safety of BT was assessed over a 5 y period following BT.

Results: 14 patients entered the long-term follow up phase. Safety measures are summarized below:

Parameter	Baseline (n=14)	Y1 (n=14)	Y2 (n=14)	Y 3 (n=14)	Y 4 (n=12)	Y 5 (n=12)
Respiratory Adverse Events/Subject*		8.4	1.4	2.4	1.7	2.4
Hospitalizations for resp. symptoms Events (no. of subjects)*	10(6)[§]	6(3)	5(4)	3(2)	1(1)	1(1)
ER visits for resp. symptoms Events (no. of subjects)*	3(2)[§]	3(3)	4(2)	0(0)	0(0)	1(1)
Pre-BD FEV1 (% pred.)[†]	63.5	69.5	70.2	69.4	68.2	70.6
Post-BD FEV1 (% pred.)[†]	75.2	78.4	79.5	78.7	80.0	79.4

[§]Patient reported for the 12 mo prior to study entry. *Not significant (Repeated measures logistic regression (% of subjects reporting the event, Year 1 to 5). [†]Not significant (Repeated measures analysis (Year 1 to 5).

There were no incidences of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or death as a result of BT treatment over the 5 y.
Conclusions: The absence of clinical complications and the maintenance of stable lung function over a 5-y period post-BT in patients with severe refractory asthma suggest long-term safety of the procedure out to 5 y.

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Efficacy of high-dose leukocytaphereis using extracorporeal circulation through a large leukocyte-removal filter column in patients with refractory asthma

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Leukocytapheresis (LCAP) as well as granulocyte and monocyte adsorptive apheresis (GMA) using extracorporeal circulation through the column has been used to treat inflammatory bowel disease and rheumatoid arthritis in Japan. We previously reported that GMA improved the peek expiratory flow rate (PEFR) in patients with severe asthma. To evaluate the efficacy of high-dose leukocytapheresis (pulse LCAP) using a large leukocyte-removal filter column (Cellsorba® CS-180S, Asahikasei Kuraray Medical, Tokyo, Japan) in patients with refractory asthma, we conducted a clinical trial. Pulse LCAP was performed 2 sessions at 1-week interval and 5 L of blood was filtered per session. The average PEFR during the 4 weeks just after the second LCAP in each patient was compared with that during the 4 weeks just before the first LCAP as a primary end point. The sum total of asthma control test (ACT) score at 4 weeks after the second LCAP was compared with that just before the first LCAP as a secondary end point. We evaluated the change of the fraction of exhaled nitric oxide (FENO) in each patient before and after pulse LCAP as a biomarker of eosinophilic airway inflammation. Five patients fulfilled the ATS criteria for refractory asthma participated in this trial up to now. The morning PEFR and the ACT score were increased in all patients. Although FENO was abnormally increased in four patients in spite of the standard therapy, it was decreased after pulse LCAP. Pulse LCAP might serve as a non-pharmacological strategy to induce clinical improvement in patients with refractory asthma through its unique anti-inflammatory effects.

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The effect of GSK2190915, a 5-lipoxygenase activating protein inhibitor, on the allergen induced asthmatic response

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Background: GSK2190915 is a potent 5-lipoxygenase activating protein inhibitor, thereby inhibiting the synthesis of leukotrienes and 5-oxo-ETE.
Objective: To assess the effect of GSK2190915 on the allergen-induced asthmatic response.
Methods: 19 eligible patients with mild asthma were enrolled and completed this 4- centre, double-blind, 2-way crossover study. They took 100 mg GSK2190915 and placebo orally once daily for 5 days, in randomised order. On Day 3 they had an inhaled allergen challenge and on Days 4 and 6 they had induced sputum collection.
Results: GSK2190915 attenuated the early (0-2 hours) and late (4-10 hours) asthmatic response to inhaled allergen compared to placebo. Following GSK2190915, the mean% attenuation of the placebo response to inhaled allergen for the minimum and weighted mean FEV_1(0-2 hours) was 33.3% and 62.6%, respectively, and the

mean% attenuation of the placebo response to inhaled allergen for the minimum and weighted mean FEV_1(4-10 hours) was 15.8% and 22.7%, respectively. There was a significant attenuation of the allergen induced increase in sputum percent eosinophil count on Day 4 following GSK2190915 compared to placebo; the treatment difference (95% CI) was -9.95% (-18.13, -1.77). There was a >90% reduction in sputum LTB4 on Days 4 and 6 following treatment with GSK2190915 compared to placebo. Median sputum LTB4 (pg/mL) was 524 and 837 on Days 4 and 6 following placebo, and 31 and 18 on Days 4 and 6 following GSK2190915. Safety and tolerability were good.
Conclusion: GSK2190915 shows potential as a treatment for asthma.
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Phase 2 randomized, double-blind, placebo-controlled study of tralokinumab, an anti-IL-13 monoclonal antibody, in moderate to severe asthma

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Backgound: IL-13 is hypothesized to be a critical mediator in the development and maintenance of the asthma phenotype.
Aim: To assess clinical activity and safety profile of tralokinumab (TK; CAT-354), a human IgG4 monoclonal antibody that specifically neutralizes IL-13.
Methods: After a 2-week run-in, 194 subjects (52% atopic) with uncontrolled moderate/severe asthma despite standard controller treatment (ACQ-6 $\geq$1.5 & $\geq$1 exacerbation in last year) received SC TK (150, 300, or 600 mg) or placebo (PBO) every other week (7 doses) in addition to continued controller treatment. The primary endpoint was change in mean ACQ-6 score at week 13 (combined TK groups vs PBO); secondary endpoints included prebronchodilator lung function and rescue β_2-agonist use.
Results: At baseline mean (SD) age was 47 yr (10.8), ACQ-6 score was 2.7 (0.6), prebronchodilator FEV_1 was 2.0 L (0.6). At week 13 mean (SD) ACQ change was -0.76 (1.0) TK vs -0.61 (0.9) PBO (*P*=0.375). Increases from baseline in FEV_1 and FVC (table) together with reduction in mean (SD) β_2-agonist use (puffs/d) of -0.68 (1.5) TK vs -0.10 (1.5) PBO (*P*=0.02) were observed following TK.

Week 13 Spirometry: Mean (SD) Change from Baseline

	Placebo (n=42)	Tralokinumab			
		150 mg (n=44)	300 mg (n=49)	600 mg (n=44)	Combined (n=137)
FEV_1 (L)	0.06 (0.48)	0.16 (0.35)	0.21 (0.37)	0.26 (0.41)	0.21 (0.38)
*P**		0.299	0.102	0.041	0.072
FVC (L)	0.00 (0.55)	0.18 (0.45)	0.12 (0.46)	0.21 (0.54)	0.17 (0.48)
*P**		0.100	0.261	0.082	0.059

**P* vs PBO.

No serious adverse events were considered drug-related by investigators.
Conclusion: Adding tralokinumab to existing controllers was associated with an increase in FEV_1 but no improvement in ACQ score.

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Efficacy of an anti-IL13 monoclonal antibody, lebrikizumab, in adults with inadequately controlled asthma is enhanced in those with high periostin levels

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Introduction: IL13 is a key mediator in asthma pathogenesis. We evaluated lebrikizumab (LB) efficacy in adults with asthma inadequately controlled by inhaled corticosteroids (ICS). We prospectively evaluated whether LB was more efficacious in participants (prts) with increased IL13-driven inflammation, measured by the serum biomarker periostin.
Methods: Phase II study of 180 adults with asthma inadequately controlled by ICS, randomized 1:1 to LB (n=88) or placebo (PB; n=92). The primary outcome was change in forced expiratory volume/second (FEV_1) from baseline (BL) to Week (Wk) 12. Secondary outcomes included change in FEV_1 from BL to Wk 24 and rate of severe exacerbations (SE) in the 24-wk treatment period. Prts with BL periostin levels above the median value were classified as "periostin-high" (PH).
Results: Compared with PB prts, mean improvement in FEV_1 from BL was 6% greater in LB prts (95% CI 1%, 11%) at Wk 12 and 5% (95% CI 0%, 9%) greater at Wk 24; the rate of SE was 51% lower in LB prts (0.11 vs 0.23 events/24 wks, 95% CI –33%, 82%). FEV_1 improved significantly in PH-LB prts compared with PH-PB prts: 11% greater at Wk 12 and 7% greater at Wk 24. PH-LB prts had 81% fewer SE than PH-PB prts (0.04 vs 0.22 events/24 wks, 95% CI –17%, 97%). The overall rate of serious adverse events was 5%; none were attributed to study drug.
Conclusions: Lebrikizumab had a clinically meaningful benefit in prts with asthma inadequately controlled by ICS, especially among PH prts with greater IL13-driven inflammation. No drug-associated safety signals were identified.

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NVA237 once daily reduces the percentage of patients with exacerbations of COPD and associated hospitalizations: The GLOW1 trial

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Introduction: COPD exacerbations, especially those leading to hospitalization, have a significant impact on patients' quality of life and long-term prognosis. We examined the influence of the once-daily (QD) long-acting muscarinic antagonist NVA237 (glycopyrronium bromide) on exacerbations of COPD.
Methods: Patients with moderate-to-severe COPD were randomized (2:1) to double-blind NVA237 50 µg QD or placebo (PBO) via a low-resistance single-dose dry powder inhaler (Concept1 device) for 26 wks. In addition to bronchodilation (primary efficacy endpoint was trough FEV_1 at 12 wks), the effect on COPD exacerbations and related hospitalizations was assessed using a Cox regression model.
Results: 822 patients were randomized; 80.5% completed. Mean age was 63.9 yrs, mean post-bronchodilator FEV_1 54.6% predicted (FEV_1/FVC 0.5). Compared with PBO, NVA237 significantly prolonged the time to first moderate/severe COPD exacerbation (hazard ratio [HR] 0.69, 95% confidence interval [CI]: 0.50–0.949; p=0.023) and the time to first severe COPD exacerbation leading to hospitalization (HR 0.35, 95% CI: 0.141–0.857; p=0.022). NVA237 also significantly reduced the percentage of hospitalizations due to COPD exacerbation (odds ratio [OR] 0.34; p=0.024). NVA237 numerically reduced the rate of moderate/severe exacerbations with NVA237 vs PBO (0.43 vs 0.59/yr; rate ratio [RR] 0.72; p=0.071).
Conclusion: In patients with moderate-to-severe COPD, compared with placebo, NVA237 50 µg once daily significantly prolonged the time to first moderate/severe COPD exacerbation and reduced the percentage of hospitalizations due to a COPD exacerbation.

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Pleiotropic effects of add-on atorvastatin therapy during the treatment of COPD patients

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The potential role of statins in treating COPD is controversial and it is unclear what anatomic COPD lesions statins affect. We have performed a prospective study to compare Atorvastatin 40mg once daily for three months in thirteen COPD patients (8 ex-smokers (ExSm) and 5 current smokers (CurrSm)). Transbronchial lung biopsy was carried out at baseline and after treatment. Twelve subjects, 11 males and 1 female, mean age 64,58 (min 56, max 78) completed the study and 48 paired biopsies were available for analysis. Lung function and cardiopulmonary exercise tests, SGRQ, 6MW test, and Holter EKG monitoring were performed, and serum lipids and hs-CRP were measured. Lung biopsy specimens were processed for histology, immunohistochemistry with anti CD45, CD11b, P-selectin, ETAR, and ET-1 antibodies. 8-isoprostane levels and differential cell count were measured in induced sputum.
Results: Symptoms significantly improved. There was no significant change in FEV1, but IC improved (In CurrSm: from 55,54% predicted (%) to 64,4%, p<0.01, in ExSm: from 81,93% to 89,9%, p<0.05, before and after therapy, respectively). TGV decreased from 119,92% to 113,69%, p<0.05, and RV/TLC improved in ExSm: from 44,01% to 40,07%, p<0.05 before and after therapy, respectively). In lung biopsies there were significant decreases in inflammatory cells numbers, CD45+ cells decreased in CurrSm: from 64,12% to 30.40%, p<0.05 and in ExSm: from 61,40% to 18,94%, p<0.05 before and after treatment, respectively. The expression of CD11b, P-selectin, ETAR, and ET-1 were also decreased after therapy. These data indicate that atorvastatin may have potential beneficial effects in COPD patients through an anti-inflammatory mechanism.

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Beta-blockers in chronic obstructive pulmonary disease – A retrospective cohort study

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Background: Beta-blockers are avoided in COPD patients.
Objectives: We examined the use of beta-blockers and their relationship with established stepwise pharmacological managements for COPD assessing their effects on mortality, exacerbations and pulmonary function.
Methods: Retrospective cohort study using a disease specific database of COPD patients (TARDIS) linked to NHS databases providing information on hospital admissions, drug prescriptions and death. Adjusted Hazard ratios were calculated through Cox Proportional Hazard Regression after correction for covariates, including history of overt cardiovascular disease.
Results: 5,977 patients, mean follow up 4.35 years, mean age 69.1 years, 88% of beta-blockers were cardio selective. There was a 22% overall reduction in all-cause mortality with beta-blocker use. Furthermore there were additive benefits of beta-blockers on all-cause mortality at all COPD treatment steps. Compared to controls the adjusted hazard ratio (95%CI) for all-cause mortality was 0.28 (95%CI, 0.21 to 0.39) for inhaled corticosteroid + long acting beta-agonist + long acting anti-muscarinic + beta-blocker verses 0.43 (95%CI, 0.38 to 0.48) without beta-blocker. There were similar trends showing additive benefits of beta-blockers in reducing oral steroid use and respiratory hospital admissions. Beta-blockers had no deleterious impact on FEV_1 or FVC at all treatment steps when given with a LABA or LAMA.
Conclusions: Our study suggests beta-blockers may reduce mortality and exacerbations when added to established inhaled stepwise therapy for COPD, independently of overt cardiovascular disease and cardiac medications, and without adverse effects on pulmonary function.