52. Exacerbations of asthma and COPD: assessment, impact and novel treatments

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Once-daily QVA149 significantly improves lung function and symptoms compared to twice-daily fluticasone/salmeterol in COPD patients: The ILLUMINATE study

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Background: QVA149 is a novel dual bronchodilator combination of the LABA indacaterol and the LAMA NVA237 (glycopyrronium), in development for the treatment of COPD. QVA149 once daily (QD) vs salmeterol/fluticasone (SFC) twice daily (BID) was evaluated in moderate-to-severe COPD patients with no history of exacerbations in the previous year.
Methods: In a double-blind, double-dummy, parallel-group study, 523 patients (QVA=258, SFC=264) were randomized to receive QVA149 110/50 μg QD (via the Breezhaler device®) or SFC 500/50 μg BID (via the Accuhaler device®) for 26 weeks.
Results: Mean age was 63 years; mean post-bronchodilator FEV_1 60% predicted. Mean FEV_1 $AUC_{0–12h}$ at Day 1 and Weeks 12 and 26 (primary endpoint) was significantly higher with QVA149 vs SFC ($p<0.001$ for all comparisons; table).

Table 1

	Least squares mean treatment difference (mL)		
	Pre-dose trough FEV_1	Peak FEV_1	FEV_1 $AUC_{0–12h}$
Day 1	–	70*	70*
Week 12	90*	150*	120*
Week 26	100*	150*	140*

*$p<0.001$.

Serial spirometry showed significantly higher and clinically meaningful improvements in FEV_1 with QVA149 vs SFC at all timepoints from 5 min to 12 h at Day 1 and Weeks 12 and 26 ($p<0.001$). QVA149 significantly improved the Transition Dyspnea Index score vs SFC (treatment mean: 2.16 vs 1.41, respectively; p=0.003), reduced rescue medication use (–0.39 puffs/day; p=0.019) and improved other lung function measures (table) over 26 weeks. The safety profile of QVA149 was similar to that of SFC.
Conclusion: QVA149 QD provided significant, sustained and clinically meaningful improvements in lung function vs SFC BID over 26 weeks, with significant symptomatic benefits.

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Accuracy in assessment of acute asthma needs improved to avoid potential adverse outcomes

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Introduction: Despite comprehensive BTS Asthma Guidelines (2011 revision), there are up to 1200 deaths annually in the UK, 90% due to identifiable and preventable disease, management and psychosocial factors. We retrospectively compared management of acute asthma admissions in a city centre hospital for 1 year (2010) with BTS guidelines to identify key areas for service improvement.
Results: Data was obtained for 72/106 admissions. The majority of admissions were female (70.8%), during winter months (63.9%), and outside normal working hours (65.3%; fig 1A). Initial peak expiratory flow rate (PEFR) and severity guide management decisions. While 79.2% had a best previous PEFR documented, pre- and post treatment PEFR were recorded in only 65.3% and 36.1% respectively. No severity was recorded in 68.1% and there was a tendency to underestimate it (fig 1B). In spite of this 91.7% of admissions were appropriate according to BTS criteria (fig 1C) and there were no subsequent deteriorations resulting in

Figure 1A Admission demographic data

Total admissions		72
Sex	Male	21/72 (29.2%)
	Female	51/72 (70.8%)
Mean age (yrs)		40
Season	Jan-Mar	25/72 (34.7%)
	Apr-June	12/72 (16.7%)
	July-Sept	14/72 (19.4%)
	Oct-Dec	21/72 (29.2%)
Time of admission	Working Day (9am-5pm)	28/72 (38.9%)
	Evening (5pm-9pm)	19/72 (26.4%)
	Nightshift (9pm-9am)	25/72 (34.7%)
Mean stay (days)		3.65 (range 0-14)

Figure 1B Severity at presentation

Severity	Recorded / 72	Retrospective / 72
None	49 (68.1%)	1 (1.4%)
Mild	4 (5.6%)	4 (5.6%)
Moderate	6 (8.3%)	24 (33.3%)
Moderate/severe	2 (2.8%)	
Severe	9 (12.5%)	31 (43.1%)
Life threatening	2 (2.8%)	11 (15.2%)
Near fatal	0	1 (1.4%)
Death	0	0

Figure 1C Appropriate admissions

Total admissions		72
Appropriate admission? (BTS guidelines)	Yes	66/72 (91.7%)
	No	6/72 (8.3%)

Figure 1D Use of IV magnesium sulphate

IV magnesium used (BTS guidelines)		12/72 (16.7%)
Used appropriately	Yes	9/12 (75%)
	No	3/12 (25%)
Not used appropriately	Yes	57/60 (95%)
	No	3/60 (5%)

death. Magnesium sulphate is often used to treat severe asthma, and was used appropriately in 75% of patients (fig 1D).
Conclusions: In keeping with previous data (Heaney, BTS adult asthma audit 2010) initial PEFR and severity, key aids to decision making in acute asthma, were routinely not recorded or underestimated. The importance of accurate initial assessment in acute asthma needs to be reinforced to avoid potential adverse outcomes.

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Impact of a single chronic obstructive pulmonary disease (COPD) exacerbation on lung function decline: Analysis of UPLIFT®
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Background: Frequent COPD exacerbations are linked to rapid decline in lung function. Little is known about the impact of a single exacerbation on rate of decline.
Aims and objectives: To examine the effect of a single COPD exacerbation on rate of decline in lung function, using data from a 4-y, randomized, double-blind, placebo-controlled trial of tiotropium in moderate-to-very severe COPD (UPLIFT®).
Methods: Retrospective analysis of annual rate of decline in pre- and postbronchodilator (BD) forced expiratory volume in 1s (FEV_1) and forced vital capacity (FVC), before and after first COPD exacerbation (increase in/new onset of >1 respiratory symptom lasting ≥3 days and treated with antibiotic/systemic corticosteroids). Eligible patients (pts) had ≥3 pulmonary function tests (PFTs) before (≥24 days after treatment start) and ≥3 months after the exacerbation (no further exacerbations permitted for next 3 PFT measurements). Rate of decline was calculated by linear regression and *P*-values by Wilcoxon signed-rank test.
Results: 462 pts were eligible (mean age 64 y, 78% male, mean baseline FEV_1 1.19 L and FEV_1/FVC 0.44). Mean annual rate of decline in pre- and post-BD FEV_1 and pre-BD FVC significantly increased (Table).
Conclusion: A single exacerbation can lead to a significantly larger rate of decline in lung function in COPD pts 1-2 years post exacerbation.

	Mean Rate of Decline mL/year, median (Q1, Q3) First exacerbation		*P*-value
	Before	After	
Pre-BD FEV_1	–27.5 (–101.1, 49.5)	–48.7 (–134.1, 22.2)	0.0006
Post-BD FEV_1	–27.8 (–97.0, 41.7)	–59.0 (–132.7, 15.7)	0.0002
Pre-BD FVC	–54.9 (–202.5, 99.8)	–61.1 (–230.3, 94.2)	0.0403
Post-BD FVC	–58.6 (–187.3, 92.4)	–65.5 (–216.6, 61.2)	0.0775

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Aclidinium bromide reduces COPD exacerbations as defined by healthcare utilisation and EXACT: Results from ATTAIN
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Introduction: COPD exacerbations can lead to considerable morbidity and mortality.
Aims: ATTAIN investigated the effect of twice-daily (BID) aclidinium bromide, a long-acting muscarinic antagonist, on exacerbations in patients with moderate to severe COPD.
Methods: In this 24-week, randomised, double-blind trial, 819 patients (mean±SD FEV_1 56.8±12.8% predicted) received aclidinium (200 μg or 400 μg) BID or placebo. Prior exacerbation history was not an inclusion criterion. Exacerbations were assessed by healthcare resource utilisation (HCRU; increased symptoms on ≥2 consecutive days requiring a change in treatment) and the EXAcerbations of Chronic pulmonary disease Tool (EXACT; persistent increase in total score of ≥9 points for ≥3 days or ≥12 points for ≥2 days).
Results: EXACT captured more exacerbations per patient per year than HCRU (EXACT: 1.0, 0.98 and 1.39 for aclidinium 200 μg, 400 μg and placebo, respectively; HCRU: 0.43, 0.40 and 0.60, respectively). Exacerbation rates were significantly lower for both aclidinium doses compared with placebo and rate ratio differences were: EXACT: 200 μg, 0.72 [p=0.017] and 400 μg, 0.71 [p=0.012]; HCRU: 200 μg, 0.72 [p=0.043] and 400 μg, 0.67 [p=0.020]; corresponding to a rate reduction of about 28% with aclidinium using each method.
Conclusions: More than twice as many events were recorded using EXACT compared with HCRU. Aclidinium 200 μg and 400 μg BID reduced exacerbations compared with placebo as assessed by HCRU and EXACT. The proportional improvement observed with treatment was similar irrespective of the method used.
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Increased risk of mortality in COPD patients using tiotropium respimat vs. tiotropium Handihaler
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Background: Tiotropium is a long-acting, once daily anticholinergic drug that is delivered via Handihaler (dry powder inhaler) or via Respimat (soft mist inhaler). Data from RCTs suggest that use of tiotropium Respimat is associated with an increased risk of mortality.
Objectives: To explore the risk of mortality in users of either tiotropium Handihaler or tiotropium Respimat.
Methods: Within the IPCI database, a Dutch GP database, we defined a source population of patients > 40 years with at least 1 year of follow-up. The study ran from 2008 to 2011. Patients were followed from start of the study until the patient died or end of follow-up. Date and cause of death were verified for all patients. From the source population, we defined a cohort of tiotropium users (Handihaler and/or Respimat) and created episodes of use. To assess the risk of dying, we considered a 30-day carry-over effect. The risk of mortality was calculated using a Cox proportional hazard regression analysis. Crude and adjusted HRs were calculated with corresponding 95% CI.
Results: From the source population, we defined a tiotropium cohort of 11,287 users providing 24,540 episodes of use. 496 patients died while being exposed to either Handihaler or Respimat. Use of Respimat was associated with an increased risk of dying (HR_{crude} 1.52, 95% CI 1.24-1.87) and this association remained upon adjustment (HR_{adj} 1.33, 95% 1.07-1.65). The association was strongest for incident users and cardiovascular or cerebrovascular death, but due to low numbers not longer statistically significant (HR_{adj} 1.87, 95% CI 0.74-4.73).
Conclusions: Use of tiotropium Respimat vs tiotropium Handihaler is associated with a 30% increase of mortality.

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The anti-IL-17A-antibody secukinumab does not attenuate ozone induced acute airway neutrophilia in healthy volunteers

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Background: Interleukin-17 (IL-17 or IL-17A) is linked to neutrophilic airway inflammation.
Aim and Objective: To evaluate the effect of a novel anti-IL-17A antibody secukinumab (AIN457) on ozone-induced airway neutrophilia in healthy volunteers.
Methods: 24 healthy volunteers with normal neutrophil levels in sputum and a proven inflammatory response to ozone 24 and 48 hours after the baseline ozone challenge (3 hours intermittent exercise with inhalation of 250 ppb ozone during the challenge) were randomized to secukinumab (10mg/kg bodyweight) or placebo or an open label prednisolone (50mg) arm in the ratio 2:1:1. Secukinumab or placebo was administered as an infusion whereas prednisolone was administered as an oral tablet. Sputum analyses were performed 24 and 48 hours following ozone challenges during the treatment phase at various time-points. Safety and pharmacokinetics were also assessed.
Results: Administration of secukinumab was safe and well tolerated. Compared to placebo, secukinumab did not attenuate ozone-induced sputum neutrophilia 24 and 48 hours after ozone challenge. Prednisolone treatment resulted in an increase of neutrophils in sputum and in peripheral blood. No immunogenicity with secukinumab was observed. Mean half life of secukinumab was 29.8 days.
Conclusions: Neutralizing IL-17A by secukinumab did not attenuate acute ozone-induced airway neutrophilia in healthy subjects. Study of the effects of anti-IL17A treatment on chronic neutrophilic airway diseases may be warranted in patients with disorders characterized by airway neutrophilia.
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Reductions in exacerbations with omalizumab in a real-world setting

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Asthma exacerbations are a major cause of morbidity and mortality. Omalizumab (OMA) reduced exacerbations in clinical trials. The 2-year, global, observational eXpeRience registry was initiated to collect data from OMA-treated allergic (IgE-mediated) asthma patients (pts), and to assess whether results from clinical trials apply in real-life practice. The intent-to-treat population included 916 pts (734 and 643 evaluable pts at Month 12 and 24, respectively). In the 12 months prior to inclusion in the registry, only 11.8% of pts were exacerbation free; at months 12 and 24, 54.9% and 65.8% of pts, respectively, were exacerbation free over the prior year.
Compared with the 12-month pre-treatment period, clinically significant and severe clinically significant asthma exacerbations decreased over time following OMA initiation (Table).

	Baseline 12 months pre-treatment (N=916)	Month 12 (N=734)	Month 24 (N=643)
Clinically significant exacerbations*			
Mean ± SD‡	4.9±5.32	1.0±1.85	1.6±2.74
Exacerbations per patient-month	0.41	0.09	0.07
Severe clinically significant exacerbations†			
Mean ± SD‡	2.2±2.80	0.2±0.75	0.3±1.02
Exacerbations per patient-month	0.18	0.02	0.01

*Clinically significant worsening of asthma requiring rescue oral/IV corticosteroids. †Clinically significant asthma exacerbations plus a reduction in PEF to <60% predicted or personal best. ‡Data are cumulative. Although means increase with longer observation time, data represent a decrease in the rate of exacerbations following OMA initiation.

These real-world data and safety profile are consistent with results from clinical trials. OMA reduces clinically significant and severely clinically significant exacerbations in pts with uncontrolled persistent allergic asthma.

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Improvement in asthma severity and control by voriconazole and posaconazole in severe asthma with fungal sensitization (SAFS) and ABPA

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Rationale and Objectives: There is growing evidence linking asthma severity with fungal allergy. We assessed the effect of voriconazole or posaconazole therapy on asthma control and severity (GINA criteria) among patients with SAFS and ABPA.
Methods: We conducted a retrospective review of adult asthmatic patients with either ABPA or SAFS receiving voriconazole or posaconazole. Clinical, radiological and immunological evaluation was used to assess response. Voriconazole (300-600 mg/day) or posaconazole (800 mg/day) (adjusted by plasma level monitoring) was given for at least 6 months, if tolerated.
Results: There were 26 patients, ABPA (n =21, severe=17) or SAFS (n = 5), 11 males, median age = 59 yrs. Eighteen of 24 (75%) discontinued oral corticosteroids, 12 of them within 3 months of therapy. Asthma severity was downgraded from severe to moderate (n=8) and moderate to mild (n=1) in 9 of 24 (38%) patients. There was a marked reduction in OCS and SABA use, health care utilization due to asthma and improvement in overall health status. Furthermore, there was a statistically significant reduction in immunological markers appearing at 9 months (p=0.008) for total IgE and at 12 months for RAST IgE Aspergillus fumigatus (p=0.0056). Six of 23 (26%) patients on voriconazole had AEs requiring discontinuation before 6 months compared to none on posaconazole (p=0.15). Four relapsed (57%), one at 3 months and 3 at 12 months after discontinuation.
Conclusion: Both voriconazole and posaconazole are effective treatment options which can improve asthma control and severity, though larger prospective studies are required are required.