45. Mechanisms and outcomes of infective exacerbations of COPD

195

Late-breaking abstract: Moxifloxacin (MXF) vs amoxicillin/clavulanic acid (AMC) in acute exacerbations of COPD (AECOPD): Results of a large clinical trial with a novel endpoint

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Introduction: Evidence-based therapy of AECB/COPD is limited by a lack of appropriate trials. MAESTRAL compares antibiotic therapies for AECOPDs in patients with moderate-to-severe disease at risk of poor outcomes.
Method: This was a multiregional, prospective, randomised, double-blind study of patients ≥60 years, FEV1<60% predicted, with an Anthonisen type 1 exacerbation and ≥2 exacerbations in the last year. Patients were stratified by systemic steroid use and received MXF 400 mg PO qd (5 days) or AMC 875/125 mg PO bd (7

days). The primary endpoint was clinical failure 8 weeks post-therapy (PP) and the study was powered for superiority (ITT).
Results: At 8-weeks post-therapy MXF was non-inferior to AMC (Table). In microbiologically confirmed AECOPD, MXF resulted in lower clinical failure and higher bacterial eradication (Table). Steroid-treated patients had worse outcomes overall; this effect was lower for MXF vs AMC. Clinical cure at 8 weeks post-therapy was significantly higher in MXF patients with eradication vs persistence at EOT (P<0.0001) but not in AMC patients (P=0.149) (Table).

	MXF n/N (%)	AMC n/N (%)	95% confidence interval (P value)
Clinical failure[‡]			
PP*	111/538 (20.6)	114/518 (22.0)	−5.89, 3.38 (n/a)
ITT	138/677 (20.4)	146/675 (21.6)	−5.50, 3.03 (0.57)
PP with pathogens	50/260 (19.2)	68/261 (26.1)	−15.0, −0.75 (0.03)
ITT with pathogens	62/327 (19.0)	85/335 (25.4)	−13.9, -1.44 (0.02)
Bacteriological failure[‡]			
PP with pathogens	89/260 (34.2)	103/261 (39.5)	− 14.9, 1.58 (0.12)
ITT with pathogens	109/327 (33.3)	125/335 (37.5)	−12.6,1.92 (0.15)
Clinical failure by steroid use[‡]			
With steroids			
PP	48/182 (26.4)	62/189 (32.8)	−15.7, 2.77 (0.17)
ITT	65/236 (27.5)	76/239 (31.8)	−12.6, 3.67 (0.28)
Without steroids			
PP	63/356 (17.7)	52.329 (15.8)	−3.65, 7.49 (0.50)
ITT	73/441 (16.6)	70/436 (16.1)	−4.4, 5.4 (0.83)
Early bacteriological result correlated to late clinical result (ITT with pathogens)			
Bacteriological result	**Clinical success at 8 weeks post therapy**		
Eradication at EOT	86/107 (80.3)	63/87 (72.4)	n/a
Persistence/superinfection at EOT	50/90 (61.1)	68/108 (62.9)	n/a

AMC: amoxicillin/clavulanic acid; EOT: end of therapy; ITT: intent-to-treat; MXF: moxifloxacin; PP: per protocol

*Noninferiority margin = 6%
‡At 8 weeks post-therapy

Conclusion: Both drugs had good efficacy. At the 8-week endpoint, MXF was superior to AMC in microbiologically confirmed AECOPD. Bacterial eradication and clinical success were strongly correlated. The results may help physicians optimise antibiotic therapy in moderate-to-severe AECOPD.

196

Rhinovirus infection induces secondary bacterial infection in COPD

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Aim: To investigate the relationship between rhinovirus infection and secondary bacterial infection.

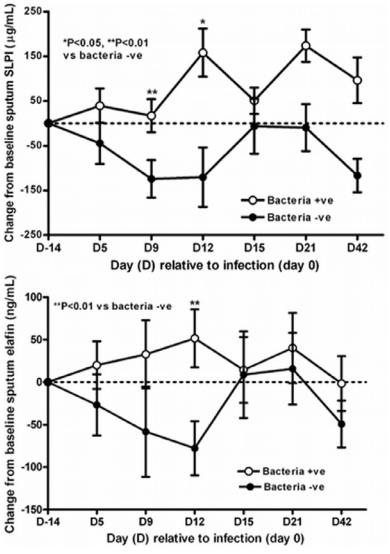

Figure 1

Methods: We performed experimental rhinovirus (RV) infection in COPD subjects (GOLD stage II, N=20), smokers with normal lung function (SMK, N=21) and non-smokers (NS, N=11). Sputum was collected at baseline and following inoculation. RV infection was confirmed with PCR and semi-quantitative bacterial culture performed. SLPI, elafin and neutrophil elastase (NE) were measured in sputum by ELISA.
Results: 1 subject with bacteria in baseline sputum was excluded. Following RV infection bacteria were detected in 65% of COPD, 19% of SMK and 30% of NS (P=0.0086). 92% of bacteria in the COPD group were pathogenic bacteria, compared with 50% in SMK and 33% in NS (P=0.045). Peak sputum virus load was on day 5 and peak bacterial load on day 15. Following RV infection sputum SLPI and elafin fell from baseline in the bacteria+ve subjects and increased in the bacteria-ve subjects.
Peak virus load (8.4±0.72 vs 6.5±0.6 copies/mL,P=0.049) and sputum NE on day 9 (0.65±0.14 vs 0.31±0.07µg/mL, P=0.026) were higher in subjects with bacterial infection compared to those without.
Conclusions: Secondary bacterial infection is common following rhinovirus infection in COPD and is associated with higher virus loads and NE, but lower levels of SLPI and elafin in sputum. Degradation of SLPI and elafin by NE may be a mechanism of increased susceptibility to bacterial infection.

197

Predictors of poor outcome in severe hospitalised COPD exacerbations

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Background: The aim of study was to determine predictors of poor outcome in patients hospitalised for exacerbation of chronic obstructive pulmonary disease (ECOPD).
Methods: Hospitalised patients with ECOPD were included in a prospective study and followed for 1 month. Clinical and epidemiological parameters were evaluated including COPD Severity Score (COPD-SS) and Charlson Index. Poor outcome was: death, intensive care unit (ICU) admission, need for mechanical ventilation (MV), prolonged hospital stay (>11 days) and emergency room (ER) visit/readmission during follow-up.
Results: 155 patients: mean age±standard deviation 70±9.5yrs; 84% men; 96% smokers/ex-smokers; 76% GOLD stage III or IV; mean hospital stay 8.8±5.5days. 69 patients (45%) had poor outcome: 4 (3%) died; 16 (10%) had ICU admission; 33 (21%) had MV, 32 (21%) had prolonged hospital stay and 24 (16%) had ER visit/readmission during follow-up. Univariate analysis identified variables associated with poor outcome: exacerbations and hospitalisation for ECOPD in the last year (p=0.033 and 0.039 respectively); lower FEV1 (p=0.004); GOLD stage (p=0.049); lower pH (p<0.001); lower PaO_2/FIO_2 (p=0.006); higher $PaCO_2$ (p<0.001); higher COPD-SS (p=0.016); long-term O_2 therapy (p=0.042). Independent predictors of poor outcome determined by multivariate analysis: number of exacerbations in the previous year (1 ECOPD: p=0.012, odds ratio [OR] 4.1, 95% confidence interval [CI] 1.4 to 12.3; ≥2 ECOPD: p=0.005, OR 4.4, 95% CI 1.6 to 12.5); pH (p=0.006, OR 0.2, 95% CI 0.1 to 0.7); $PaCO_2$ (p=0.015, OR 1.3, 95% CI 1.1 to 1.7).
Conclusion: Previous exacerbations, hypercapnia and respiratory acidosis were identified as predictors of poor outcome in patients with severe ECOPD.

198

Human respiratory epithelial cells acquire a long-lasting antiviral condition when exposed to interferon beta

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Type I interferons (IFNs) induce strong antiviral effects and are therefore attractive to prevent seasonal respiratory infections or reduce the incidence of virus-mediated exacerbation in COPD patients. Yet, clinical application of type I IFNs is hindered due to significant side effects observed during repetitive use. In this study we investigate the duration of protection, mediated by prophylactic IFNbeta, against a human rhinovirus (HRV) infection.
Human respiratory epithelial (A549) cells were exposed for 18 hours to various concentrations (31-500 IU/ml) of IFNbeta. Then, IFNbeta was either removed or maintained in the supernatant for the rest of the experiment. Next, cells were infected with HRV-1B (MOI 0.1) at t = 0, 24, 48, 72 or 168 hours after the initial exposure to IFNbeta. At 48 hours post infection, the protective effect of IFNbeta on HRV-induced cell death was determined by a colorimetric assay. RT-qPCR and plaque assay were used to determine HRV infection.
In the continuous presence of IFNbeta, 90-100% of A549 cells were protected against HRV-induced cell death at every time point and at all IFNbeta concentrations. This strong protective effect was confirmed by RT-qPCR and plaque assay. Alternatively, when IFNbeta was removed, cell death increased with time and in dose-dependent way. Nevertheless, at 168h post IFNbeta stimulation (500IU/ml), still 75% of all cells were viable.
These data show that IFNbeta has not only a strong, but also long-lasting protective effect against HRV-1B. This opens new opportunities for prophylactic treatment of viral respiratory infections without the risk of side effects often seen after repetitive and systemic use.

199

Rhinovirus infection upregulates pentraxin-3 in smokers and COPD patients

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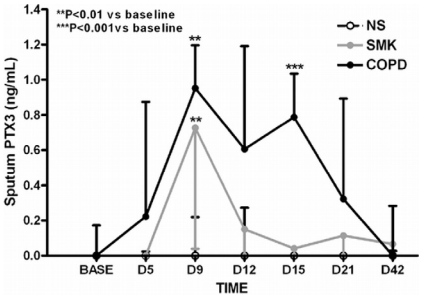
Pentraxins are a family of acute-phase reactants and pentraxin-3 (PTX3) is the prototypic long pentraxin. PTX3 has a protective role against pathogens including influenza viruses and both pro- and anti-inflammatory actions of PTX3 are described. The role of PTX3 in virus-induced COPD exacerbations is unknown.
Methods: We infected 3 groups of subjects–COPD GOLD stage II (N=20), smokers with normal lung function (SMK,N=21) and non-smokers (NS,N=11)–with rhinovirus (RV). Induced sputum was collected on 6 time points post-inoculation, cytospins prepared and cell counts determined. PTX3 and neutrophil elastase (NE) were measured in sputum supernatants by ELISA and sputum virus load by quantitative PCR.
Results: Following RV infection PTX3 in sputum was significantly increased over baseline in the COPD group and the SMK but not the NS.



PTX3 levels were higher in the COPD group compared to the NS on days 9, 12, 15 and 21 and compared to the SMK on day 15. Peak sputum PTX3 levels correlated with peak sputum virus load (P=0.0002, r=0.51), peak total sputum inflammatory cells (P=0.0002, r=0.50) and peak sputum neutrophil elastase levels (P=0.0006, r=0.47).
Conclusions: PTX3 may be an important mediator of neutrophilic inflammation following RV infection in COPD subjects and smokers. PTX3 is likely to contribute to the inflammatory response in virus-induced COPD exacerbations and may be both a potential biomarker and therapeutic target in COPD.

200

Metagenomic analysis of lower airway microbial diversity in patients with chronic pulmonary disease

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Aim: To identify microorganisms unrecognized through culture in the lower airway of patients with chronic pulmonary disease through amplification and pyrosequencing of specific genes for microbial diversity assessment
Method: To avoid culture-related bias, 1) DNA extraction from respiratory samples (sputum, bronchial aspirate (BAS), bronchoalveolar lavage (BAL) and bronchial mucosa); 2) 16S rRNA amplification and purification with modified primers which include a specific 8 nucleotides code per sample; 3) Pyrosequencing of amplified products by Titanium/GS-FLX System (454-Roche; 4) Obtention of >500 sequences per sample; and 6) Comparison of the results obtained with the diferent samples using bronchial mucosa as gold standard.
Results: Sputum, BAS, BAL and bronchial mucosa samples from 6 patients were studied. Over 500 sequences of gen 16S were identified in 17 out of 24 samples. Total number of bacterial genera per patient were over 100. Analysis of coincidence obtained from bronchial mucosa showed low coincidence with BAS and sputum, and maximal coincidence with BAL, that showed a range of 55-74 bacterial genera. Streptococcus, Prevotella, Moraxella, Haemophilus, Acinetobacter, Fusobacterium and Neisseria were the most often identified genders, accounting for up to 60% of the overall.
Conclusions: Pyrosequencing is applicable to samples of bronchial secretions and is able to demonstrate a microbial diversity over 600 microorganisms. Sputum and BAS samples were non-representative of bronchial mucosa, but BAL that mostrates over fifty bacterial genera, shows the closest results with bronchial mucosa.
Sponsorship by Fundacio Parc Tauli.

201

Value of galactomannan in bronchoalveolar lavage fluid for invasive pulmonary aspergillosis in critically ill chronic obstructive pulmonary disease

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Backgroud: Critically ill COPD patients who require ICU admission are at particular risk of invasive pulmonary aspergillosis (IPA).
Objective: To investigate the value of galactomannan (GM) in BALF for rapid diagnosis and prognosis of IPA in critically ill COPD patients.
Design: We investigated the clinical data of patients with severe COPD in RICU of Beijing Chaoyang Hospital from February 2009 to December 2009 prospectively. Patients were divided to proven, probable, possible, colonization and non-IPA group. Serum GM and BALF GM were done at the first day of RICU admission.
Results: 50 patients were recruited in the study,and 34 patients had BALF samples which were classified as probable IPA, possible IPA (n=6), 2 colonization (n=2) and non-IPA group (n=17); According to the ROC curve, when chose 0.795 as the cut-off of BALF GM test, the sensitivity, specificity, positive and negative predictive value for probable IPA were 88.9%, 95.1%, 100% and 93.7%, respectively;All of the patients of IPA group were dead. The result of GM test in BALF with IPA group were mush higher than control group (2.88 vs 0.49, p=0.009). The mortality was mush higher in the patients whose GM test in BALF above 0.795 than the patients lower 0.795 (80% vs 17% p=0.001);
Conclusions: Compare to serum GM and aspergillus culture, GM in BALF prove to be more useful in early diagnosis of IPA with critically ill COPD patients. 0.795 maybe a best cut-off in BALF GM detection. Besides,high GM value in BALF was associated with high mortality in a certain sense.

202

WITHDRAWN