Biomarkers in stable and acute exacerbations of COPD

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CHAPTER 8

Summary

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In **chapter 2** we presented the results of the CATCH trial (CRP-guided Antibiotic Treatment in acute exacerbations of COPD admitted to Hospital). In this trial patients hospitalized with an acute exacerbation COPD were randomized to receive antibiotics based according the GOLD strategy (patient reported sputum purulence) or according to the CRP (≥50 mg/L) strategy. Hundred and one patients were randomized to the CRP-group and 119 to GOLD-group. Fewer patients in the CRP-group were treated with antibiotics 31.7% compared to 46.2% in the GOLD-group (p=0.028) (adjusted OR 0.178; 95%CI 0.077-0.411). Thirty-day treatment failure rate was equal (CRP-group 44.5% vs GOLD-group 45.5%; (p=0.881) (adjusted OR 1.146; 95%CI 0.649-1.187) as was time to next exacerbation (CRP-group 32 days, versus GOLD-group 28 days (p=0.713) (adjusted HR 0.878; 95%CI 0.649-1.187). Length of stay was similar in both groups (CRP-group 7 days versus GOLD-group 6 days (p=0.167). On day 30 no difference in symptoms score, quality of life or serious adverse events was detected. In the present study no differences between both groups in adverse events were found. Based upon our results we concluded that the use of CRP as a biomarker to guide antibiotic treatment in severe AECOPD leads to a significant reduction of antibiotic treatment without compromising safety profile. Further research is needed for the generalizability of these findings.

In **chapter 3** we presented the results of a post-hoc analysis of 207 patients included in the CATCH trial. In this study we analysed the impact of blood eosinophils (≥2% of total white cell count and absolute eosinophil count ≥300 cell/microliter) at admission on clinical outcome in patients with severe AECOPD. Thirty-nine (18.8%) had eosinophilia ≥2% and 23 patients (11.1%) had a peripheral blood eosinophil counts ≥300cell/microliter. Eosinophilia was associated with shorter median length of stay in the eosinophilic groups (≥2% or ≥300 cell/microliter) compared to the non-eosinophilic groups. Early treatment failure (within 10 days) was reduced in both the eosinophilic groups (≥2% or ≥300 cell/microliter). Late treatment failure (day 11-30) was equal in the eosinophilic groups as well as in the non-eosinophilic groups. Relapse (day 31-180), was more frequent in both eosinophilic groups (≥2% or ≥300 cell/microliter), but in the latter group this did not reach statistical significance. Eosinophilia ≥2% was associated with a lower risk factor for having early treatment failure (HR 0.339; 95%CI 0.122-0.943) whereas eosinophilia ≥2% was a risk factor for having relapse (eosinophilia ≥2%: HR 2.351; 95%CI 1.335-4.139). We concluded that blood eosinophilia in patients with hospitalized AECOPD at admission is associated with higher short-term treatment success. However, blood eosinophilia ≥ 2% predicts a less favourable outcome on the long term.

In **chapter 4** we presented the result of a sub-study of the CATCH trial. In this exploratory study patients with severe AECOPD, in whom pneumonia was excluded using chest X-ray, underwent additional LDCT-thorax. C-reactive protein (CRP), Procalcitonin (PCT), and Serum Amyloid A (SAA) on admission were assessed and correlated with potential CT abnormalities. Of the 100 patients that were included, 24 patients had one or more radiographic abnormalities suggestive for pneumonia. The inter-observer agreement between two readers (Cohen's Kappa) was 0.562 (95%CI 0.371-0.752 p<0.001). Biomarkers were significantly higher in the group with CT abnormalities compared to group without: CRP was 20.5 (IQR 8.8-81.5) mg/L and 76 (IQR 21.5-148.0) mg/L (p=0.018), PCT was 0.06 (IQR 0.04-0.08) µg/L ando 0.09 (IQR 0.06-0.15) µg/L (p=0.007), SAA was 16 (IQR 3-89) µg/ml and 95 (7-160) µg/ml (p=0.019), respectively. The sensitivity and specificity of all three biomarkers where poor for detecting pneumonia by LDCT in this population. The area under the ROC curve was 0.659 (95% CI: 0.521-0.796) for CRP, 0.664 (95%CI: 0.526-0.801) for PCT, and 0.687 (95%CI: 0.566-0.808) for SAA. We concluded that in quarter of patients with severe AECOPD without infiltrate(s) on the chest X-ray, additional infiltrative changes compatible with acute-phase lung involvement were detected by LDCT. Although the three investigated biomarkers were significantly higher in the group with abnormalities present on LDCT, they were not able to reliably detect or exclude CAP in this specific population.

In **chapter 5** we presented the results of the validation study of the COPD-lower respiratory tract infections – visual analogue score (c-LRTI-VAS). The questionnaire was validated in patients with stable COPD as well as those with an acute exacerbation of COPD (AECOPD). The results of c-LRTI-VAS were compared with two health related quality of life questionnaires (St Georges Respiratory Questionnaire (SGRQ) and Clinical COPD Questionnaire (CCQ)). Validity, reliability and responsiveness were assessed. Eighty-eight patients with clinically stable COPD and 102 patients who had an AECOPD completed the c-LRTI-VAS questionnaire. When testing on two separate occasions for repeatability, no statistically significant difference between total scores was found 0.143 (SD 5.42) (p=0.826). Internal consistency was high across items Cronbach's Alpha 0.755. Correlation with SGRQ and CCQ total scores was moderate to high. After treatment for hospitalized AECOPD, the mean c-LRTI-VAS total score improved 8.14 points (SD 9.13; p=<0.001). We concluded that the c-LRTI-VAS showed proper validity, responsiveness to change and moderate to high correlation with other questionnaires. It therefore appears a reliable tool for symptom measurement in COPD.

In **chapter 6** we present the results of an exploratory double blind randomized controlled trial investigating the effect of a 3-week course of doxycycline on sputum and systemic inflammatory parameters in stable COPD patients presumably without

bacterial colonisation of the airways. The effect of doxycycline treatment on inflammatory markers (TNF-α, IL-1β and IL-6) and neutrophil specific markers in sputum (MPO, MMP's, and IL-8) and serum C-reactive protein was evaluated. Sputum was obtained by sputum induction with hypertonic saline. A total of 41 patients were included. Ten patients were excluded as they were not able to produce sputum at the first or second visit. Baseline characteristics were similar in the two groups. In the remaining patient's doxycycline did not influence sputum MPO concentrations. Also, MMP-8 and 9, IL-6 and IL-8 concentrations as well as lung function parameters were not affected by doxycycline. Systemic inflammation by means of CRP was also not influenced by doxycycline. Based upon our study we cannot recommend doxycycline for the reduction MPO sputum levels nor any of the other inflammatory sputum and systemic markers.