Stable state MR-proadrenomedullin is associated with severe exacerbations in COPD

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ABSTRACT

Background: Midrange-proadrenomedullin (MR-proADM), assessed in stable COPD patients, has been shown to be associated with all-cause mortality. However, the association of stable state MR-proADM with severe exacerbations of COPD requiring hospitalisation (severe AECOPD), or with community acquired pneumonia (CAP) in COPD patients has not been studied yet.

Aims and objectives: The aim of this study was to evaluate the association of stable state MR-proADM with severe AECOPD and CAP in COPD patients.

Methods: This study pooled data of 1285 patients from the COMIC and PROMISE-COPD cohort studies. Time till first severe AECOPD was compared between patients with high (≥ 0.87 nmol/l) or low (< 0.87 nmol/l) levels of plasma MR-proADM in stable state as previously defined. For time till first CAP, only COMIC data (n=795) was available.

Results: COPD patients with high level stable state MR-proADM had a significantly higher risk for a severe AECOPD compared with those with low level MR-proADM with a corrected hazard ratio (cHR) of 1.30 (95% CI, 1.01 - 1.68). Patients with high level stable state MR-proADM had a significantly higher risk for a CAP compared with COPD patients with low level MR-proADM in univariate analysis (HR 1.93; 95% CI, 1.24 - 3.01) but, after correction for age, lung function and previous AECOPD, the association was no longer significant (cHR 1.10; 95% CI, 0.68- 1.80).

Conclusions: Stable state high level MR-proADM in COPD patients is associated with severe AECOPD but not with CAP.

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease accompanied with increased morbidity and mortality.(1;2) Underlying chronic and systemic inflammation play an important role in the pathophysiology of COPD, its progression and its associated comorbidity.(3-6) It is estimated that COPD is the third leading cause of death worldwide.(7) COPD is characterised by acute exacerbations (AECOPD) which can accelerate the already existing gradual decline in lung function and increase the risk of death.(8;9) Furthermore, AECOPD are associated with increased risk of hospitalisation, lower quality of life and increased healthcare costs.(8;10) Effective therapy or interventions to prevent this morbidity and mortality include for instance inhalation medication, smoking cessation, supplemental oxygen therapy, pulmonary rehabilitation and lung transplantation.(11)

Nowadays, the emphasis lies more on personalised treatment and guidance of COPD patients. Where COPD is a heterogeneous disease with different phenotypes, patients with COPD are heterogeneous as well in their risk for the development of morbidity and their risk of death.(1;12;13) For the individual COPD patient predicting high risk for this morbidity and mortality may lead to changes in patient management such as adjustment of therapy and self-management or even end of life conversation.(11)

To determine risks for adverse outcomes in patients with COPD various tools have been developed, such as the multidimensional BODE-index and the ADO-score.(14;15) Different biomarkers are established to predict adverse outcomes as well. An important one is MR-proADM, the biologically-inactive midregional fragment of the adrenomedullin prohormone.

The aetiology and characteristics of MR-proADM are extensively described elsewhere.(16) In brief, MR-proADM is the more stable precursor of adrenomedullin (ADM) and is used as a surrogate for the pluripotent regulatory peptide ADM. ADM is widely expressed throughout the body and acts as both a hormone and a cytokine. It potentially has comprehensive effects such as vasodilatory, diuretic, anti-inflammatory and antimicrobial. Widespread ADM expression has been established in pulmonary tissue as well. ADM can be upregulated by hypoxia, inflammation, bacterial products and shear stress. Thus, elevated ADM levels can often be seen in end stage pulmonary disease. Due to its different properties, MR-proADM is not only used in pulmonary disease but in multiple other diseases as well such as cardiovascular disease and in sepsis.(17)

MR-proADM measured in stable state has been shown to be associated with survival in COPD patients(18) and to be an independent predictor when combined with the BOD and ADO with which the predictive power of the indices even increased.(19) However, the association of stable state MR-proADM with morbidity in COPD has not been studied yet. Community acquired pneumonia (CAP) and severe AECOPD resulting in a hospitalisation are among the most important factors contributing to this morbidity and are associated with a high burden of disease and low quality of life.(20)

The aim of this study was to evaluate the association of stable state MR-proADM with morbidity in COPD patients, defined as risk of severe AECOPD and CAP. To assess the association we used data of two large European prospective observational cohort studies of patients with COPD in stable state, the COMIC and the PROMISE-COPD study.

Methods

Settings and study population

For this study we performed a pooled analysis of individual patient data of two large European prospective observational COPD cohort studies, the COMIC study (Cohort of Mortality and Inflammation in COPD) and the PROMISE-COPD study (PRedicting Outcome using systemic Markers In Severe Exacerbations of Chronic Obstructive Pulmonary Disease). Detailed inclusion and exclusion criteria of both studies are included in the supplemental material.

Outcomes

The outcome parameters were time till first hospitalisation for an AECOPD and time till first CAP. For time till first CAP only data from patients included in the COMIC study were available. AECOPD was defined as an acute negative change from baseline, reported by the patient, in dyspnoea and/or sputum volume and/or colour of sputum (yellowish or greenish sputum) and/or cough, which may warrant additional treatment of prednisolone with or without antibiotics by a physician in a patient with underlying COPD. Pneumonia was defined as an acute respiratory tract illness associated with radiographic shadowing on a chest radiograph consistent with infection which was neither pre-existing nor of any other known cause.⁽²¹⁾ All X-rays were double read by a radiologist and a chest physician. In case of doubtful shadows in the report, the X-ray was presented to another chest physician for final judgment.

MR-proADM

Plasma samples of MR-proADM were obtained at stable state and levels were measured with an automated sandwich immunoassay using a time-resolved amplified cryptate emission technology (TRACE).(22) Stable state is defined as the moment in which no exacerbation occurred and no prednisolone or antibiotics were used for a minimum of 4 weeks before the blood sample was taken. MR-proADM level was dichotomised as high (≥ 0.87 nmol/l) or low level (< 0.87 nmol/l) as defined in an earlier study with the pooled cohorts.(19)

Statistical analysis

Continuous variables are expressed as mean ($\pm$ standard deviation (SD)) or as median (interquartile range (IQR)), and categorical variables as counts (percentages). Time from inclusion to event (first hospitalisation for a severe AECOPD, first CAP) was analysed by Kaplan-Meier survival curves and compared between COPD patients with high (≥ 0.87 nmol/l) or low (< 0.87 nmol/l) level of MR-proADM with log rank tests. Univariate and multivariate Cox proportional hazard regression models were used to establish the association of MR-proADM with time till first hospitalisation for an AECOPD and time till first CAP. First we studied in univariate analyses the association between MR-proADM and potential confounders within the baseline characteristics such as lung function parameters, previous AECOPD in the year before inclusion, GOLD stage, body mass index (BMI), comorbidity, and sex. Next, we studied in multivariate Cox proportional hazard regression models the association between the outcome parameters (time till first hospitalisation for an AECOPD, time till first CAP) on the one hand and MR-proADM level on the other hand, and added all confounders (i.e. variables that were associated with MR-proADM and the outcome parameter of the specific models with a corresponding p-value < 0.10). We started the

multivariate model with all confounders. Variables with the highest p-value were eliminated step by step until the fit of the model decreased significantly, based on -2 log likelihood. All tests were two-sided and a p-value of 0.05 was considered statistically significant. Data were analysed using SPSS, version 22 (SPSS Inc. Chicago IL, USA)

Results

Baseline characteristics

In 1285 out of 1433 patients from both studies MR-proADM was measured in stable state and these patients were used for the analyses. The baseline characteristics of these patients are displayed in Table 1, stratified for both studies. Median follow up times of the COMIC and PROMISE-COPD study were respectively 915 (824-1068) and 725 (421-764) days. 321 (25%) patients were defined as having a high level of stable state MR-proADM. The cumulative proportion of patients with at least one severe AECOPD in the pooled analysis and at least one CAP in the COMIC study after 1, 2 and 3 years are displayed in the Tables 2 and 3 respectively, stratified for low and high level of stable state MR-proADM.

Time till first hospitalisation for an AECOPD

In the pooled analysis COPD patients with high level stable state MR-proADM (N=321) had a significantly higher risk for a severe AECOPD compared with those with low level MR-proADM (N=964) (Figure 1) (log-rank: $p < 0.001$) with a hazard ratio of 1.56 (95% CI, 1.24 – 1.98) in univariate analysis. In the multivariate Cox regression analysis patients with high level stable state MR-proADM, corrected for the confounders FEV1 (litres), BMI, mMRC, heart failure, diabetes mellitus and previous AECOPD still had a significantly higher risk for a severe AECOPD with a corrected hazard ratio of 1.30 (95% CI, 1.01 – 1.68).

Time till first CAP

In the COMIC study COPD patients with high level stable state MR-proADM (N=197) had a significantly higher risk for a CAP compared with COPD patients with low level MR-proADM

(N=474) (Figure 2) (log-rank: $p=0.003$) with a hazard ratio of 1.93 (95%CI: 1.24 – 3.01) in univariate analysis. However, corrected for age, FEV1 (litres) and previous AECOPD in multivariate Cox regression analysis this association was no longer significant (cHR 1.10; 95% CI, 0.68 – 1.80).

Discussion

In our pooled analysis of two large European COPD cohort studies MR-proADM, measured in stable state, was shown to be an important biomarker associated with severe AECOPD. A high level of MR-proADM, measured in stable state, was associated with a 30% increased risk of a severe AECOPD when corrected for potential confounders such as lung function, previous AECOPD, age and comorbid status. With 25% of the patients having a high stable state MR-proADM level and with 34% (cumulative proportion) of the patients having at least one severe AECOPD during the 3 years of follow up, our results are not only significant but are clinically relevant as well.

In patients with COPD, exacerbations are important determinants of their quality of life, health status and disease progression. Additionally they are a major factor in the total burden of costs in COPD. The most important component of these costs are hospitalisations. Therefore, in the daily care for the COPD patient prevention of severe exacerbations of COPD is not only important for preserving quality of life, lung function, exercise performance and even preventing mortality, but it also is important for reducing healthcare costs.(8;10) Therefore, the prevention of exacerbations of COPD and the risk assessment for future exacerbations plays an important role in the management of COPD in the strategy document from the Global Initiative for Chronic Obstructive Lung Disease.(23)

Identifying patients with high risk for a severe AECOPD, for instance by high level stable state MR-proADM offers the physician an additional and strong tool to decide when to take additional measures to prevent the detrimental effects of an severe exacerbation. Different

pharmacological and non-pharmacological strategies are described and used in practice to prevent COPD exacerbations, such as bronchodilators, inhaled corticosteroids, phosphodiesterase-4 inhibitors, long term antibiotics and pulmonary rehabilitation.(10;24) However the evidence for and effect of some of these strategies are limited and may only be effective in selected patients. Besides, up until now, the choice for one or more of these treatment strategies are mostly based on clinical and lung function parameters and not based on biomarkers. Therefore, further studies should address whether biomarker guided treatment with these strategies and perhaps a more extensive monitoring of our COPD patients at high risk for a severe AECOPD favourably impacts short and long-term morbidity. In addition, up to know, it remains unknown whether the information on a low risk profile based on a biomarker-guided stratification could lead to a change in management, such as, for instance, restricting access to certain interventions.

Patients with exacerbations, especially the ones that require hospitalisation, are at increased risk of dying compared with patients who do not develop exacerbations.(8;10;20) MR-proADM at stable state is a strong predictor for mortality. The current analysis shows that increased MR-proADM at stable state is also associated with an increased risk of severe AECOPD. The higher mortality risk attributed to elevated levels of stable state MR-proADM defined in earlier studies may at least partly be because of its association with severe AECOPD. Biomarker guided prevention of severe AECOPD could therefore have the potential to lower the mortality risk as well.

Evidence accumulates that MR-proADM is associated with morbidity and mortality at different time points during the course of COPD. In stable state high MR-proADM is

associated with severe AECOPD, exertional hypoxemia(25) and mortality.(18) During exacerbation, high MR-proADM predicts length of hospital stay and mortality(17) and elevated MR-ProADM at hospital discharge predicts survival as well.(26) It would be interesting to know how the association and predictive value of MR-proADM with morbidity and mortality behaves when serial longitudinal measurements within one patient are made during the course of the disease, if changes in the MR-proADM level are followed by changes in disease activity, and if treatment (pharmacological and/or non-pharmacological) of the COPD influences MR-proADM levels. Future studies have to address these topics.

Another way in which identifying patients with a higher risk for severe AECOPD with MR-proADM could be used is by helping these higher risk patients to be included in interventional studies in COPD in which (severe) exacerbations are an important outcome. It is proposed that the enrichment of trials with these subjects at high risk may improve the power of the study, lower the number of patients needed to be included and shorten the follow-up time of the study.(27)

The cut-off level of MR-proADM used in this study was based on an earlier study.(19) However, that was a study with mortality as the end-point. To establish whether the value of 0.87 nmol/l is the ideal cut-off level for morbidity as well we performed additional analyses with different validated cut-off levels of MR-proADM used in a recent validation study.(28) The different cut-off levels did not result in a stronger association (data not shown), thus the cut-off value of 0.87 nmol/l seems to be reasonable for morbidity as well.

In our study, MR-proADM was not associated with CAP. In the general population MR-proADM measured in patients with a CAP was an independent predictor for clinical outcome including mortality and it had additive prognostic value combined with the Pneumonia Severity Index and CURB-65.(22;29-31) There is a rationale that high-levels of stable state MR-proADM could predict CAP in patients with COPD. Indeed, there was a positive association about MR-proADM and outcome, albeit not stable after adjustment for age and FEV1. It cannot be excluded that the smaller sample size could be responsible for this finding, i.e. β -error.

The patients in the PROMISE-COPD study had a slightly worse lung function, were more often current smokers and had more comorbidity than the patients in the COMIC study. Conversely, a higher proportion of the patients included in the COMIC study has been included at an acute exacerbation of COPD, a fact known to be an important predictor for a new exacerbation.(32) So, a limitation of the study is that the patients included may have a more severe COPD and are mainly controlled and treated in secondary care. Therefore the results of this study cannot automatically be extrapolated to patients with mild COPD controlled in primary care.

There are different causes for exacerbations.(10) It is debatable if one biomarker could be capable to encompass the whole complexity of exacerbations. Different biomarkers are described being associated with exacerbations (with or without hospitalisation).(33) In a recent large scale biomarker panel study using two large and well characterized cohorts by Keene et al. however many of these biomarkers were no longer associated with or predictive for exacerbations and their additive value with known predictive clinical parameters were

limited as well.(34) The role for these biomarkers to be used in COPD have therefore become uncertain. Stable state MR-proADM has never been evaluated with morbidity in COPD until now. The strength of this study include the large sample size of a well-characterized multicentric cohort from several European countries. The various established and validly assessed covariates made it possible to determine the association of stable state MR-proADM with morbidity. This study design with the pooled analysis potentiates the generalizability of stable state MR-proADM being an important biomarker associated with severe AECOPD. Future studies should address the additive value of stable state MR-proADM to known (clinical) predictors for severe AECOPD.

In conclusion, plasma MR-proADM measured at stable state in patients with COPD is significantly associated with severe AECOPD but not CAP in a large, pooled European COPD cohort. MRproADM shall be evaluated in prospective, intervention studies as a marker to identify patients requiring intensified management aiming to prevent severe exacerbation.

Table 1 Baseline characteristics of 1285 individuals with stable COPD included in this analysis

	COMIC N= 671	PROMISE-COPD N= 614	p-value
Mean age at enrolment in years (SD)	67.3 (9.5)	67.0 (9.5)	0.576
Male (number (%))	404 (60.2)	432 (70.4)	<0.001
Current smoker (number (%))	170 (25.3)	204 (33.4)	0.002
Mean Pack-years (SD) ¹	37.7 (22.9)	50.8 (29.8)	<0.001
Mean BMI at enrolment (SD) ²	27.4 (5.4)	26.0 (5.5)	<0.001
Lung function ³			
Mean FEV ₁ in litres (SD)	1.5 (0.6)	1.3 (0.5)	0.001
Mean FEV ₁ % predicted (SD)	53.6 (19.1)	49.4 (16.7)	<0.001
GOLD stage (number (%)) ⁴			<0.001
I	63 (9.4)	16 (2.6)	
II	299 (44.6)	280 (45.8)	
III	252 (37.6)	214(35.0)	
IV	56 (8.4)	101(16.5)	
Mean mMRC score (SD) ⁵	1.8 (1.3)	1.7 (1.2)	0.776
Mean BOD score (SD) ⁶	2.4 (1.8)	2.6 (1.8)	0.163
Mean ADO score (SD) ⁷	4.1 (1.8)	4.1 (1.7)	0.769
Mean updated ADO score (SD) ⁷	7.6 (2.4)	7.8 (2.2)	0.154

Comorbidities (number (%))			
Congestive heart failure ⁸	112 (16.7)	93 (15.2)	0.465
Myocardial infarction ⁹	27 (4.0)	58 (9.5)	<0.001
Diabetes mellitus ¹⁰	43 (6.4)	74 (12.2)	<0.001
Previous AECOPD (number (%)) ¹¹	265 (39.5)	274 (44.6)	0.063

¹ Pack-years of resp. 626 and 593 patients in the COMIC and PROMISE-COPD study

² BMI of resp. 658 and 612 patients

³ Lung function measures of resp. 670 and 564 patients

⁴ GOLD stage of resp. 670 and 611 patients

⁵ mMRC score of resp. 654 and 599 patients

⁶ BOD score of resp. 642 and 552 patients

⁷ ADO and updated ADO score of resp. 653 and 544 patients

⁸ Diagnosis of congestive heart failure was recorded of 612 patients in the PROMISE-COPD study

⁹ Diagnosis of myocardial infarction was recorded of 611 patients in the PROMISE-COPD study

¹⁰ Diagnosis of diabetes mellitus was recorded of 608 patients in the PROMISE-COPD study

¹¹ Minimum of 2 AECOPD or 1 severe AECOPD in the year before inclusion

Abbreviations; SD: Standard Deviation; BMI: Body Mass Index; FEV₁: Forced Expiratory Volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung disease; mMRC: modified Medical Research Council dyspnoea grade; BOD: Index that combines Body mass, airflow Obstruction (FEV₁ % predicted), Dyspnoea (mMRC); ADO: Index that combines Age, Dyspnoea (mMRC) and airflow Obstruction (FEV₁ % predicted).

Table 2 Cumulative proportion of patients having at least one severe AECOPD at 1, 2 and 3 years

Follow-up	High MR-proADM (Standard Error) N=321	Low MR-proADM (Standard Error) N=964	Total (Standard Error) N=1285
1 year	0.20 (0.02)	0.13 (0.01)	0.15 (0.01)
2 years	0.33 (0.03)	0.23 (0.01)	0.25 (0.01)
3 years	0.44 (0.04)	0.31 (0.02)	0.34 (0.02)

Table 3 Cumulative proportion of patients having at least one CAP at 1, 2 and 3 years

Follow-up	High MR-proADM (Standard Error) N=197	Low MR-proADM (Standard Error) N=474	Total (Standard Error) N=671
1 year	0.08 (0.02)	0.04 (0.01)	0.05 (0.01)
2 years	0.16 (0.03)	0.09 (0.01)	0.11 (0.01)
3 years	0.24 (0.04)	0.13 (0.02)	0.16 (0.02)

Figure legends

Figure 1 Kaplan–Meier Survival Curve for association of stable state MR-proADM with time till first hospitalization for an AECOPD.

Figure 2 Kaplan–Meier Survival Curve for association of stable state MR-proADM with time till first CAP.

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