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Review Article

Mediators of inflammation in COPD

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by an airway and systemic inflammation. The inflammatory process consist of many mediators, which contribute to the progression of disease leading to the induction of emphysema and obliteration of the small airways. In this overview we describe the result of studies investigating the key components of COPD inflammation, their association with progression of disease, the options for functioning as a biomarker, and therapeutic interventions directed on the inflammatory process.

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating disease characterized by airflow limitation, reduced lung function, breathlessness, decreased productivity, and poor quality of life. COPD is the only major disease with an estimated increasing prevalence and mortality rate in de coming decades. In 2015 COPD caused 2.6% of global DALY's, Furthermore, it is estimated that by 2030 COPD will become the fourth leading cause of death worldwide [1–5].

The inflammatory process in COPD is responsible for the induction of emphysema and obliteration of the small airways due to chronic bronchitis [6].

In this article we will discuss the pathophysiology of COPD with the focus on the different leukocytes and cytokines that play a key role in the inflammatory response of COPD in the airways and the general circulation. Interestingly, they may function as a biomarker to monitor the course or treatment of COPD.

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Progressive Markers of Inflammation

Neutrophil-related mediators: Neutrophils play a key role in antimicrobial defense, but activated neutrophils can also damage host cells and tissues. Neutrophil degranulation causes a release of inflammatory mediators like neutrophil elastase (NE), cathepsin G and proteinase 3 [7]. Neutrophil elastase is a proteolytic enzyme, capable of damaging the extracellular matrix (ECM), causing mucus gland hyperplasia and increased mucus production, reduction of ciliary beating rate and thereby causing direct damage to airway epithelium. When released into the intracellular space, NE can be present in a free and membrane bound form. A positive correlation is shown between distribution of NE within the alveolar spaces and the presence of emphysema and airway obstruction [8,9].

Interleukin 1-beta: The interleukin-1 (IL-1) family consist of 11 cytokines. These cytokines may induce a complex network of proinflammatory cytokines, which may be of importance in the pathogenesis of COPD. IL-1β for instance regulates and initiates inflammatory response via expression of integrins on leucocytes and endothelial cells. Interleukin 1β binding to an IL-1 receptor I results in further neutrophilic inflammation [10].

Interleukin-1β also possesses a strong pro-inflammatory effect [11], as IL-1β overexpression is associated with a neutrophilic infiltrate, distal airspace enlargement, airway-wall thickening and increased sputum production in patients in patients with COPD [12].

Sapey et al conducted a study to determine the levels of serum and sputum cytokines in COPD patients and healthy controls [13]. In this study 15 stable COPD patients were matched with 15 healthy controls. No differences in serum levels of IL-1β between COPD and healthy controls had been observed. Sputum IL-1β correlated significantly with sputum neutrophil and macrophage counts (Pearsons correlation coefficient (PCC) 0.83, $p<0.001$ and PCC 0.3 $p<0.02$, respectively). A negative correlation was observed between serum IL-1β and forced expiratory volume in 1 second ($r=-0.56$ $p=0.02$) [13].

Another study compared 30 COPD patients with 30 healthy controls to establish an association between serum levels of IL-1β and lung function decline [14]. Significantly higher serum IL-1β levels were found in COPD patients compared to healthy controls ($p<0.05$). A negative correlation between IL-1β levels and FEV1 was seen $r=-0.624$ [14].

A third study investigating serum IL-1β levels in 60 patients with COPD of whom 30 with an AECOPD and 30 with stable COPD found a significant difference in serum concentration compared to 20 healthy controls. Furthermore this study showed that serum IL-1β levels were higher when disease severity increased [15].

In summary, there seems to be higher concentration of serum IL-1β in patients with COPD, which could be a reflection of the pro-inflammatory state of COPD. This is also reflected by the correlation of IL-1β levels and neutrophil and macrophage counts in sputum.

Interleukin 6: Interleukin (IL)-6 is a pleotropic cytokine that acts as a pro-inflammatory mediator and acute-phase response inducer, but also possess anti-inflammatory properties. It is increasingly apparent that the airway epithelium is a major source of IL-6 in the lungs. As an anti-inflammatory role cytokine, IL-6 has inhibitory effects on Tumor Necrosis Factor-α (TNF-α) and IL-1 [16]. IL-6 can contribute to tissue destruction by deposition of matrix, antibody complexes and proteases in the targeted tissue [17].

Bhowmik et al. studied 57 patients with moderate to severe COPD. Sputum samples were analyzed both during a stable COPD period and during an acute exacerbation of COPD (AECOPD) respectively. His group observed that patients with $\geqslant 3$ exacerbations per year had higher stable median IL-6 levels than those with $\leqslant 2$ exacerbations per year (rho=0.383, p=0.01). Median IL-6 levels were higher during an exacerbation when compared to the stable COPD phase ($p<0.05$) [18].

Breath condensate IL-6 levels were analysed by Bucchioni et al. comparing 16 COPD patients with healthy non-smokers. In this study higher IL-6 levels were found in COPD patients compared to healthy non-smokers. IL-6 levels tended to increase with age in the control group but not in the COPD group. No correlation was found between IL-6 and lung function in either group [19].

Another study showed that the IL-6 mean serum values did not change significantly during a one-year period of follow up in a group of 58 stable COPD patients. Serum interleukin levels were measured at baseline and one year later, no change in FEV1 and BMI was observed. There was no statistically significant change in the measurements of serum IL-6 between both visits ($p>0.05$) [20].

Ferrari found that higher serum IL-6 levels are associated with mortality, with a hazard ratio of 2.68. 29Serum IL-6 levels were evaluated in 77 COPD patients of whom 53 were included in a follow up of 3 years. Serum IL-6 had a negative correlation with the 6-Minute Walking Distance at baseline and after 3 years. Although no causal relation was proven in this study, the association suggests a persistent deleterious effect of IL-6 on physical performances of COPD patients [21].

A meta-analysis of 33 studies, performed by Wei et al found evidence for elevated levels of serum IL-6 in COPD patients compared to healthy controls. However, no association was found between lung function decline and IL-6 levels [22]. A more recent study by Singh et al. was not included in the meta-analysis by Wei. In this study 384 COPD patients were compared with 50 healthy controls. Serum levels of IL-6 were significantly ($p < 0.05$) higher among mild, moderate, severe and very severe COPD patients. Furthermore results showed a negative correlation between serum IL-6 and FEV1, FEV1 predicted and FEV1/FVC values [23].

To summarize the studies described above, serum interleukin 6 was elevated in COPD patients compared to healthy individuals and higher sputum IL-6 levels were found during an exacerbation.

Interleukin 17: Interleukin 17 is a pro-inflammatory cytokine produced by the T-helper 17 cell. After binding to the receptor, IL-17 activates several signalling cascades that induce chemokines. Acting as chemo-attractants, these chemokines recruit monocytes and neutrophils to the site of inflammation [24].

Increased levels of IL-17 and enhanced numbers of IL-17 positive cells have been detected in the bronchial mucosa and sputum of COPD patients, as was shown by two bronchial biopsy studies [25,26]. Doe et al. compared sputum IL-17 levels between asthma and COPD patients. A significant higher IL-17 level was found in sputum from COPD patients ($P<0.0001$)[27].

The IL-17 levels in lung tissue of healthy non-smokers, smokers with normal lung function and COPD patients were examined by Zhang et al in 2010. 36This group examined IL-17 levels in lung tissue of patients who underwent a lobectomy because of pulmonary malignancy. IL 17 levels were significantly higher in smokers with normal lung function than the healthy control group. Furthermore, a significant higher level of Il-17 was found in COPD patients than in smokers with normal lung function. The levels of IL-17 in lung tissue showed a negative correlation with the FEV1 percentage of predicted value. Similar result were published by Chen et al.[28,29].

In another study serum IL-17 concentrations were examined [30]. The IL-17 levels in patients during an AECOPD were significantly higher than the levels of patients with stable COPD or healthy control group. Furthermore, the levels were positively correlated with serum C-reactive protein levels, neutrophil count and smoking status (pack-years), but negatively correlated with FEV1% predicted in COPD patients. Serum IL-1β levels were markedly positively associated with serum IL-17 levels in patients with COPD[30].

To summarize, elevated IL-17 concentrations are found in COPD according to numerous studies, and these levels are further increased during exacerbations. Elevated levels can be found in sputum, serum and lung tissue. A negative correlation has been found with spirometry variables such as FEV1.

TNF - alpha: TNF – alpha (TNF-α) is a pro-inflammatory cytokine involved in systemic inflammation and is one of the key cytokines of the acute phase reaction. TNF-α is produced in numerous cell types like activated macrophages, CD4+ lymphocytes, natural killer cells, neutrophils, eosinophils and mast cells [31]. In a systematic review Gan et al. showed that serum TNF-α levels were higher in patients with COPD than in control subjects [32]. Furthermore, these results show that increased TNF-α levels were present in sputum of COPD patients and during exacerbations [33,34].

Lin et al performed exhaled breath condensate (EBC) in 40 COPD patients and in 20 patients without COPD, pre- and post-lobectomy, because of lung carcinoma. Furthermore, the group histologically examined resected lung tissue to determine TNF-α density [35]. The EBC TNF-α levels were significantly higher in the COPD groups compared with the non-COPD group before surgery. EBC TNF-α levels correlate negatively with FEV1/FVC. 43 TNF-α content in lung tissue was significantly higher in the COPD population. The expression of TNF-α in lung tissue positively correlated with EBC TNF-α levels. A negative correlation between FEV1/FVC and expression of TNF-α in lung tissue had been observed [35].

The same result was observed by Singh et al., serum levels of TNF-α were directly proportional to the post-bronchodilator FEV1 percentage [23]. Elevated serum levels of TNF-α were found in COPD patients compared to healthy control subjects and levels seemed to increase with severity of disease [36].

In summary, the results from these above mentioned described studies showed that increased concentrations of TNF-α were present in serum, sputum and EBC of COPD patients. TNF-α levels tended to be higher in the more severe COPD stages.

Interleukin 8: Interleukin 8 (CXCL8) is a chemokine involved in inflammation-mediated neutrophil infiltration and chemotaxis [37]. Multiple cells like monocytes, alveolar macrophages, pulmonary epithelium, smooth muscle cells of the airway, eosinophils, fibroblasts and endothelial cells are its important sources [37]. IL-8 is frequently increased in patients with COPD compared to healthy controls; analysis of Broncho Alveolar Lavage (BAL) and sputum samples has also shown increased levels of IL-8 in patients with mild-to-moderate COPD compared to healthy controls [38].

A weak association has been observed between neutrophil count in induced sputum and the CXCL8 serum level [39].

Another study showed that CXCL8 levels were elevated in sputum and plasma of stable COPD patients and during an exacerbation compared to asthma patients and healthy controls. The IL-8 levels correlated with the percentage of neutrophils found in induced sputum, this is in line with a meta-analysis performed by Su et al. [40,41].

One study analysed serum IL-8 levels of patients with asthma, AECOPD or Asthma-COPD Overlap Syndrome (ACOS) and compared them with healthy subjects. The IL-8 serum level was significantly higher in the AECOPD group and ACOS group than in the asthma population. A negative correlation had been found with FEV1, FEV1%pred, and FEV1/FVC [42].

Another study analysed serum and BAL IL-8 levels in 25 patients with severe COPD, in 25 patients with moderate COPD and in 10 healthy controls. The mean value of IL-8 concentrations in BAL and serum were significantly higher in COPD patients than in the healthy controls. In severe COPD significantly higher serum IL-8 levels were measured than in the mild COPD patients [43].

Zhang et al. found significantly higher levels of serum Il-8 in patients with frequent COPD exacerbations (two or more exacerbations a year), compared with the group non-frequent exacerbators [44].

To summarize, higher IL-8 levels in sputum, BAL and serum were present in COPD patients. Serum IL-8 levels may be associated with COPD severity.

Interleukin 10: Several cell types like monocytes, macrophages, mast cells, T and B lymphocytes and dendritic cells can secrete IL-10. In the inflammatory process regulatory cytokines, such as interleukin-10 (IL-10), are essential to limit inflammation [45]. Il-10 suppresses Th1 cytokines such as IFN-γ and TNF-α and has anti-inflammatory effects on neutrophils by inhibiting IL-8 [46].

In patients with asthma and in patients with cystic fibrosis, reduced levels of Il-10 have been found in BAL fluid [47,48]. Furthermore, another study has shown that Il- 10 levels in sputum were decreased in COPD patients compared to healthy non-smokers [49].

This has also been demonstrated by Moermans et al. study in which sputum and serum of 95 COPD patients and 33 healthy subjects were analysed for the presence of IL-10. Results showed that sputum IL-10 levels were lower in COPD patients when compared to healthy subjects. Serum Il-10 was detectable in 46% of the COPD patients and in 7% of the healthy subjects, a significant difference (p=<0.01). A significantly higher level of serum Il-10 was found in patients with COPD compared to healthy subjects [50].

Pelegrino et al. examined serum and induced sputum concentrations of IL-10 in 17 active smoking COPD patients, 35 ex-smokers with COPD and 20 active smokers without COPD. The concentration of IL-10 in serum was similar in COPD and active smokers without COPD. Significant higher levels of IL-10 in sputum were found in both COPD groups compared to active smokers without COPD [51].

In a larger study by Zhang, 94 COPD patients were compared with 45 healthy controls and healthy smokers. Serum and sputum IL-10 were similar in COPD and healthy smokers. Levels of serum and sputum IL-10 were significantly lower in the healthy smokers and COPD groups, compared to the healthy non-smokers group [52].

To summarize, different results are documented by several studies investigating Il-10 levels in COPD patients. Based on the results above, there is a tendency of lower IL-10 levels in sputum of COPD patients compared to healthy subjects.

Interferon–ϒ: Interferon-ϒ (IFN-ϒ) is produced by Th1 lymphocytes and plays a key role in the host immune responses to pathogens [53]. IFN-ϒ (previously named macrophage-activating factor) has the important function to prepare the innate immune response for conditions such as infections [54]. Priming the macrophages with IFN-ϒspeeds up the response against pathogens and leading to hyper-responsiveness with an increase in cytokine release. In healthy humans, this mechanism facilitates rapid clearance of infection. However, in COPD patients it is suggested that this mechanism may also have harmful effects in terms of increased tissue damage [55].

Panzner et al. analysed IFN-ϒ mRNA expression in bronchial biopsies of 7 chronic bronchitis patients with obstruction, 7 patients with chronic bronchitis and no obstruction and 9 healthy controls. Markedly elevated levels of IFN-ϒ mRNA were found in patients with chronic bronchitis with and without obstruction, compared to the healthy controls (p=<0.01). No significant difference was found between the groups of chronic bronchitis with or without obstruction [56].

Another study examined IFN-ϒ expression in peripheral airways of 19 patients undergoing lung resection for localized pulmonary lesions [57]. Specimens from 7 smokers with COPD, 5 smokers with normal lung function, and 7 non-smoking subjects with normal lung function were analysed. Elevated production of IFN-ϒ had been measured in COPD patients when compared to smokers with normal lung function and healthy subjects.

In a study, with 81 COPD patients and 21 healthy controls by Zhu et al., IFN-ϒwas more frequently produced by the serum CD8 T cells of COPD patients than by the corresponding cells from normal subjects. A correlation with IFN-ϒproduction by CD8 cells and diseases severity was found [58].

A recent study by Mitra et al. showed increased levels of serum IFN-ϒ in 30 smokers diagnosed with COPD, compared with 20 smokers without COPD. This finding is in line with previous results. A significant negative correlation with FEV1/FVC was found [59].

In summary, elevated levels of IFN-Ywere found in lung tissue and serum in patients with COPD.

MMP-9: Matrix metalloproteinase 9 proteins are involved in the breakdown of extracellular matrix, which occurs in emphysema.

Elevated serum and sputum levels of MMP-9 were associated with FEV1 and TLCO decline. In a study by Higashimoto et al. baseline levels of several biomarkers (including MMP-9) were measured in 96 COPD patient [60]. MMP-9 serum level was significantly higher in the rapid decliners group (FEV1 decline >3%/year) compared to the non-rapid decliners. A significant negative correlation between MMP-9 and FEV1% predicted and FEV1 (L) was found (r=-0.288 and r=-0.354 respectively). No significance was found with other lung function parameters. In a study by Culpitt et al. median MMP-9 levels (in sputum) were increased 8.5 fold above healthy non-smoking controls, 6.5 fold above asthmatics and 4 fold above healthy smokers, all results were significantly different [61]. MMP-9 correlated negatively with FEV1 (p=<0.001) and a positive correlation was found with the percentage and number of neutrophils in sputum (P=<0.001).

In 19 COPD patients MMP-9 sputum levels significantly increased during an exacerbation compared to samples collected in stable COPD. Levels of MMP-9 during exacerbation correlated significantly with both neutrophil and lymphocyte counts [62].

In a study by Paone et al., sputum levels of MMP-9 were found to be elevated in COPD patients (n=42) compared to symptomatic smokers (n=42) without obstructive pulmonary disease [63]. There was no correlation with lung function parameters. Levels of MMP-9 were significantly higher in the COPD group compared to the group of symptomatic smokers without obstruction. No significant difference in MMP-9 sputum levels were found between severe and mild COPD subjects.

In a population based study, spirometry had been performed and serum levels MMP-9 were measured in 888 elderly participants (aged >70). Lower FEV1 values were significantly associated with higher serum levels of MMP-9 [64].

An inverse correlation with MMP-9 serum levels and FEV1 was also found in a study, in which 80 women with COPD and 40 healthy women were analysed [65].

Kyoung Koo et al. analysed serum MMP9 in 57 COPD patients and 36 normal controls. MMP-9 levels were negatively correlated with FVC (r=−0.23), and levels of MMP-9 were inversely correlated with FEV1 (r=−0.24). MMP-9 correlated with the emphysema index [66].

In summary, the performed studies showed that levels of MMP-9 were elevated in sera and sputa of patients with COPD. Several studies showed inverse correlations between MMP-9 levels and lung function.

Predicting Markers of Inflammation

Eosinophil-related mediators: Eosinophils are a particular kind of leukocytes, mainly known for their role in allergic disease and defence against parasites. Under certain conditions eosinophils migrate to tissues to facilitate inflammatory reaction by release of chemokines, cytokines and cytotoxic granular products. COPD can as well be characterized by an eosinophilic airway inflammation. Sputum eosinophilia can be seen in 20-40% of patients with COPD. Eosinophil proteins (eg. Eosinophilic Cationic Protein (ECP), Eosinophil Peroxidase (EPO) and eosinophil derived neurotoxin) are toxic to bronchial epithelial cells [67,68]. The exact role of eosinophils in the pathogenesis of COPD is unknown [69-71]. Brusselle et al. described in a review that higher blood eosinophil levels may predict an increased risk of future exacerbations. Also treatment response to corticosteroid therapy may be predicted by eosinophil blood levels [72-74].

Desmosine: Desmosine is a special amino acid unique to mature cross-linked elastin in humans, responsible for elasticity in several organs (e.g. the lungs). When elastin is damaged, desmosine will be released. Because of increased breakdown of elastin in COPD/emphysema it may be hypothesized that elevated levels of desmosine can be found. Therefore, it may be a suitable biomarker for COPD and probably have prognostic characteristics. [75-80].

Several studies aimed on the usefulness of desmosine concentrations in serum. Lindberg et al. analyzed desmosine in urine and plasma in healthy controls and COPD patients. A total of 349 urine and 318 plasma samples were analysed. Urine samples of 234 healthy controls were compared with 115 urine samples of COPD patients (67 COPD GOLD 1, 43 COPD GOLD 2, 5 COPD GOLD 3, respectively). Concentrations of urine desmosine correlated significantly with all lung function measures. Adjusted for age and sex, 1 standard deviation of urine desmosine (0.86 nmol $mmol^{-1}$ creatinine) corresponded to ~3% units lower FEV1 % predicted and about 1 $mlmin^{-1}mmHg^{-1}$ lower $_{DL,CO}$. Mean urine desmosines levels adjusted for age and sex were 2.63, 2.49, 2.94 and 2.73 nmol mmol-1 creatinine for the healthy controls, COPD GOLD1, COPD GOLD 2 and COPD GOLD 3 group respectively. Plasma desmosine negatively correlated with forced expiratory volume in 1s and DLCO (p=<0.05) [76].

Chalmers et al. examined serum desmosine levels in 92 COPD included in the COLUMBUS trial [81]. Baseline desmosine levels did not correlate with risk of exacerbations or time to first exacerbation. Desmosine levels at baseline and during an acute exacerbation were analyzed in 24 patients, in which there was no significant difference between stable condition and exacerbation [82].

In a different study by Rabinovich et al., desmosine levels were found in subjects with cardiovascular disease and in COPD patients with cardiovascular disease [77]. No correlation was found in this study between desmosine levels and emphysema, emphysema progression or FEV1 decline. Desmosine levels were related to cardiovascular comorbidity, atherosclerosis, systemic inflammation and predicted all-cause mortality.

In a study performed by Huang et al., significantly elevated plasma desmosine levels were found in COPD patients compared to non-smoking and smoking healthy controls and smoking and non-smoking asthma patients [83]. During an exacerbation the plasma desmosine levels did no differ significantly with the levels measured during stable COPD. Urine desmosine levels increased significantly during an exacerbation, but remained normal during stable COPD.

Significantly elevated levels of desmosine were found in urine, sputum and plasma of COPD patients compared to healthy controls by Ma [75]. Urine desmosine samples were analyzed in 11 COPD patients and compared to healthy controls. Plasma levels were analyzed

in 14 COPD patients and compared to 4 healthy controls. Sputum levels were analyzed in 8 COPD patients and compared to 5 healthy controls

To summarize, desmosine levels are increased in plasma of COPD patients. However, no difference in desmosine concentrations has been measured between a stable COPD state and exacerbation. A negative correlation between lung function and desmosine levels is documented.

Pro-adrenomedullin: Adrenomedullin (ADM) is a peptide hormone [84]. The ADM belongs to the calcitonin gene peptide superfamily: calcitonin, PCT, the calcitonin gene-related peptide (CGRP), amylin and ADM. ADM molecule has a 27% similarity to CGRP [85].

The gene for human ADM, located to a single locus on chromosome 11 consists of 4 exons and 3 introns. The mRNA encodes the information for synthesis of a preprohormone known as preproadrenomedullin, which is subsequently degraded into proadrenomedullin (pro-ADM) by cleaving the signal peptide. The proadrenomedullin has three vasoactive peptides, the ADM, the aminoterminal peptide of proadrenomedullin (PAMP) and adrenotensin. There is also a region without known activity, the midrange-proADM. Pro-adrenomedullin is a stable peptide and it is a more suitable biomarker than adrenomedullin itself, given its longer half-life of several hours and 20 to 30-fold higher peak levels in comparison to plasma adrenomedullin [86-89]. Adrenomedullin is a pluripotent regulatory peptide acting as both a hormone and a cytokine. It has extensive vascular, immunomodulatory and metabolic effects, like leukocyte migration, controlling electrolyte balance[89,90]. Adrenomedullin also possesses antimicrobial features, having a direct bactericidal activity by the modulation of complement activity [91,92].

One study investigated pro-ADM levels in 167 patients admitted to the hospital for an AECOPD [93]. Measurement of plasma pro-ADM took place at admission, after 14-18 days and after 6 months. During admission the pro-ADM levels were significantly higher compared with recovery and stable phase. Pro-ADM independently predicted 2-year survival. Pro-adrenomedullin plasma levels > 0.84 nmol/l on hospital admission was significantly associated with an increased mortality risk within 2 years from 13 to 32% [93].

Another study analyzed serum pro-ADM in 85 patients with a variety of pulmonary diseases (e.g. COPD, asthma, sarcoidosis, lung-cancer) and compared it with peak VO2 (ml/kg/min). In this study serum pro-ADM was associated with a lower peak VO2 [94].

In a study by Zuur-Telgen et al, plasma pro-ADM levels were determined in 181 patients during a stable state and at hospitalization for an AECOPD when they also produced sputum [95]. Patients with COPD and pro-ADM levels of >0.71 nmol/L in the stable state had a threefold-higher risk of dying compared with levels <0.71 nmol/L . The corrected Odds Ratio for 1-year mortality was 8.90 in patients with high pro-ADM levels measured in the stable state, compared with patients with low levels measured in the stable state. Patients hospitalized for an AECOPD with high median levels of pro-ADM (above 0,79nmol/L) on admission had a shorter survival time compared to COPD patients with lower pro-ADM levels. The 1- and 2-year RR for mortality of COPD patients with low versus high pro-ADM levels were 4, 10 and 2, 26 respectively [95].

In a large European study containing 638 patient with COPD (PROMISE-COPD cohort) 549 (86.1%) patients were analysed to compare pro-ADM, BODE index and components, alone or together to predict 1-year and 2-year all-cause mortality [96]. Pro-ADM was significantly associated with 1-year mortality (4.7%) and 2-year mortality (7.8%) and comparably predictive to BODE regarding both mortality outcomes. Relative to using BODE alone, adding pro-ADM significantly improved 1-year and 2-year mortality prognostication (C statistics 0.750 and 0.818, respectively). Pro-ADM plus BODE was more predictive than the original BODE including 6-min walk distance[96].

A study by Citgez et al. with pooled data of 1285 patients showed that COPD patients with high levels of stable state pro-ADM had a significantly higher risk for a severe AECOPD compared with those with lower levels of pro-ADM during a three year follow up [97].

Several studies have been conducted regarding pro-ADM. Pro-ADM may be a suitable biomarker for predicting survival. Higher levels of plasma pro-ADM are correlated with an increased mortality risk. Higher levels of stable state pro-ADM correlate with a more severe AECOPD phenotype. An association was found with peak VO2.

Discussion and Future

The inflammatory response is mainly present in the airways, but also in the systemic circulatory system, in which many cytokines are involved[7,32]. These cytokines form a complex interaction. It is therefore difficult to identify one excellent biomarker for COPD.

Ideally, a biomarker must associate closely and consistently with a health outcome of interest (e.g. in COPD: rate of decline in lung function over time, exacerbation frequency or mortality). The biomarker should have a biologically plausible role in the pathogenesis of COPD. The biomarker should be modifiable with interventions that are known to improve health outcome in COPD [98].

Predicting: During an exacerbation of COPD elevated levels of the pro-inflammatory IL-1B, IL-8, TNF-α, pro-ADM, MMP-9 are found in serum and sputum. Those levels are significantly increased during an exacerbation, compared to stable state COPD, making it a plausible biomarker to diagnose an exacerbation.

Another pro-inflammatory biomarker IL-6 was elevated serum and sputum of COPD patients. Significant higher levels are found during an exacerbation. Higher median levels are correlated with more frequent exacerbations as was shown by Bhowmik et al. Interestingly is the ability of IL-6 to predict the risk of upcoming exacerbations. Also pro-ADM may be capable of predicting frequent exacerbations.

Progression: Cytokines that may predict lung function decline were serum IL-1B, IL-6, IL-17 and IFN-γ.

Serum desmosine and MMP-9 also showed an inverse correlation with lung function decline in several studies. Pro-ADM correlated with 1 and 2 year mortality risk.

Therapy: Novel therapies directed on specific cytokines involved in the inflammatory process of COPD are developed. Rennard et al. studied the efficacy and safety of infliximab, an anti -TNF alpha antibody, in 79 patients with COPD compared to 77 COPD patients receiving placebo [99]. This study showed that there was no clinical

benefit between the patients treated with infliximab compared to placebo, which was evaluated with the Chronic Respiratory Questionnaire and lung function outcome parameters. It was argued that the duration of treatment was limited to 6 months, which might be too short to demonstrate a significant clinical effect. Another possible explanation may be that treatment was not assigned to COPD patients with high levels of TNF-α. Till now, there are no data available of COPD patients with elevated TNF-α levels, who may benefit from treatment with infliximab.

A randomized placebo-controlled trial with anti-IL-1 receptor monoclonal antibodies (MEDI8968) was performed by Calverley et al [100].

A total of 164 COPD patients were randomized to placebo and 160 to MEDI8968. No improvement in disease was shown (exacerbation rate, lung function and quality of life). Also in this study the levels of the targeted interleukins were not measured on beforehand, possibly selected patients might have benefited from this therapy.

A possible other treatment option is the reduction of neutrophil elastase activity in COPD patients. Several NE-inhibitors have been produced (e.g. nebulized or systemic alpha-1 antitrypsin (α1-AT); NE inhibitors AZD9668; and several others) and some have been tested in COPD patients. Two phase IIb RCTs with AZD9668 were performed in COPD patients. One RCT contained 615 patients (placebo (N=302), AZD9668 60 mg bid (N=313). AZD9668 didn't show a beneficial effect on lung function: change in mean pre-bronchodilator FEV1 versus placebo was 0.01L (p=0.533). Also AZD9668 didn't significantly improve respiratory signs and symptoms, SGRQ-C score or time to first exacerbation [101]. The other RCT contained 838 patients. They were randomized to AZD9668 5 mg bid (212 patients), 20 mg bid (206 patients), 60 mg bid (202 patients) or placebo (218 patients). AZD9668 didn't show effect on lung function, respiratory signs and symptoms, QoL or biomarkers. At end of treatment, the change in mean pre-bronchodilator FEV1 for AZD9668 60 mg bid compared with placebo was 0.00L (p=0.873) [102]. The only positive effect of NE-inhibition was seen in the RAPID trial [103]. In this trial 93 patients with an α1-AT deficiency and severe emphysema received intravenous augmentation therapy and 87 received placebo during 24 months [104]. The intravenous augmentation treatment had a positive effect on the rate of loss of lung parenchyma without an effect on exacerbation frequency or survival.

Conclusion

Pro-ADM may be the best biomarker for predicting exacerbation and mortality prognosis in COPD. Further research to this peptide should be performed before implementing this marker in clinical practice.

Novel treatment strategies aimed at certain cytokines involved in the inflammatory process of COPD don't seem to fulfill the expectations yet. Further research is warranted regarding cytokine targeted therapy, in which selection of patients based on cytokine levels should be the next step.

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