Chapter 8

Conclusions, general discussion and implications

Introduction

Chronic obstructive pulmonary disease (COPD) is highly prevalent and one of the most common causes of chronic morbidity and mortality world-wide [1]. The WHO (World Health Organisation) predicts an increase in COPD-related deaths in the up-coming years [2]. In the past, COPD has been viewed as an irreversible and untreatable disease. However, in the most recent decades, research has focused increasingly on COPD and current research offers a more optimistic point of view.

COPD is a heterogeneous disease characterised by airway symptoms, impaired quality of life, enhanced airflow limitation, emphysema and extra-pulmonary co-morbidities that vary interindividually in expression and severity. Airway inflammation is widely accepted to be the central feature of COPD, leading to destruction of lung parenchyma, goblet cell hypertrophy and tissue remodelling. Because of the complexity of the disease, it is important that the goal for therapy focuses on these multiple components.

This thesis focuses on clinical phenotyping in COPD and effects of therapy on various components of the disease including: health status, chronic bronchitis, the effects of inhaled corticosteroid and long-acting bronchodilator drugs on airway inflammation, clinical phenotypes and the decline in FEV_1, predictors of the effects of therapy and monitoring of daily self-reported symptoms and lung function. The Groningen Leiden Universities and Corticosteroids in Chronic Obstructive Lung Disease (GLUCOLD) study was a prospective longitudinal, randomised, double blind, placebo-controlled two-centre trial. Patients were randomly assigned to receive either fluticasone propionate (500 µg bid) or placebo for 2.5 years. The main conclusions are presented below, followed by a general discussion and directions for future research.

Conclusions

Clinical symptoms and airway inflammation

- Airflow limitation, other features previously associated with asthma, *i.e.* bronchodilator reversibility, total serum IgE and airway hyperresponsiveness and airway inflammation are distinctive, largely independent components of COPD (**Chapter 2**).
- Airway inflammation independently contributes to impaired health status in COPD: the larger the percentage of sputum macrophages, the more impaired health status was (**Chapter 3**).
- Chronic bronchitis reflects an inflammatory sub-phenotype among patients with moderate to severe COPD that is characterised by a distinct inflammatory cell profile in sputum and bronchial biopsies. The presence of chronic bronchitis is associated with a differential distribution of eosinophils in the airway wall and sputum, and higher percentages of macrophages in sputum (**Chapter 4**).

Long-term therapy with inhaled fluticasone propionate, with and without salmeterol

- Long-term inhaled steroid therapy can provide prolonged anti-inflammatory efficacy in COPD, associated with attenuated decline in lung function. Our results suggest that disease progression may be slowed in subgroups of steroid-naïve patients with moderate to severe COPD (**Chapter 5**).
- Patients with fewer pack years smoking, preserved diffusion capacity of the lung, limited hyperinflation, and lower number of total cells in induced sputum benefited most from inhaled corticosteroids. In addition, higher number of total cells and neutrophils in induced sputum, appeared to be predictive of a more effective reduction of the number of $CD3^+$ in bronchial biopsies by treatment with fluticasone during 30 months. This suggests that COPD patients expressing milder and/or earlier stages of the disease or a subtype of COPD patients in whom airway obstruction is less determined by emphysema can benefit from anti-inflammatory therapy, which favours a differential approach in the treatment of COPD (**Chapter 6**).
- Long-term treatment with inhaled corticosteroids improves patient-reported day-to-day general and functional health status in patients with moderate to severe COPD, whereas stopping fluticasone at 6 months worsens daily health status, symptoms, functional performance and peak

expiratory flow (PEF) Combination of ICS and a long-acting ß$_2$-agonist improves initial additional positive effects on health status, functional performance and PEF. Part of self-monitored outcomes were clinically relevant (**Chapter 7**).

Heterogeneity of the disease

It is widely recognized that COPD is a complex syndrome with irreversible airflow limitation that is associated with airways inflammation, but is also characterised by different pulmonary and extra-pulmonary components. Previous large epidemiological studies examined COPD patients as a distinct, but single disorder. However, it is now time to look further than just regarding all COPD patients as having the same disease and to focus on assessing the complexity of the syndrome of COPD. Remarkably, in June 2012 a PubMed-based literature search produced 1059 hits when searching for papers on "COPD phenotype or subgroup" amongst the 35,942 papers that are dealing with COPD. The data in the present thesis provides good evidence that COPD phenotyping is clinically relevant, strongly suggesting that phenotyping will improve current clinical practice and individualised treatment options [3-10].

In chapter 2 we have examined the heterogeneity in COPD by factor analysis. This analysis was used to categorise various clinical and inflammatory characteristics into specific independent domains of the disease without *a priori* assumptions. Airflow limitation, features previously associated with asthma (bronchodilator reversibility, total serum IgE and airway hyperresponsiveness) and airway inflammation were distinctive, largely independent components of COPD. Previous studies focused primarily on clinical features [11;12], whereas we extended these findings by distinguishing a separate domain for airway inflammation. Interestingly, there was a distinct domain for 'asthma-like' characteristics. These features have been suggested to be linked to the progression of the disease. However, in chapter 6 we have seen that these characteristics were not predictive of the effects of therapy on the decline in FEV_1, indicating that these characteristics may reflect different components in COPD than in asthma. This fits with modern views on the phenotypic characteristics that are discriminating (and sometimes are shared) between asthma and COPD [13].

Health status

The most important features from the patients' perspective are worsening of airway symptoms, limited physical activity and psychological distress,

resulting in decreased health status. Patients seek medical help with their clinical physician to feel better and clinicians will probably try to positively influence the distress with life-style advises or medical therapy. So, why should we bother about time-consuming measurements such as lung function, airway hyperresponsiveness, hyperinflation or even worse, invasive measurements such as induced sputum or bronchial biopsies? Reason for this is that clinical meaningful outcomes such as symptoms in COPD cannot easily be used as surrogate markers for the underlying components of the disease. It is well-known that health status is only marginally associated with FEV_1 and the effect of therapy on health status can be influenced by many other aspects of the disease such as older age [14]. If medical therapy is able to modify the underlying process of the disease, and hence can slow down the progression of the disease this will be an important reason to provide therapy, even in the absence of distressing symptoms.

One of the main components in COPD is airway inflammation. In our study, we examined whether there is an association between health status and inflammatory cell counts in induced sputum and bronchial biopsies (Chapter 3). Health status as measured with the SGRQ, was associated with higher inflammatory cell counts in induced sputum. Worse total SGRQ scores as well as the subdomains “symptom” and “activity” scores were associated with higher percentages macrophages in sputum. Patients with <15% macrophages had a total score of 27 and this score was worse by >4 points in patients with >15% macrophages, which exceeds the clinical threshold in SGRQ that is considered to be clinically relevant [15]. Interestingly, the inflammatory process was a stronger determinant of health status than other physiological measurements. Only hyperinflation showed a consistent independent influence on health status. Expiratory airflow limitation in COPD increases the time that lungs need to fully empty. With increasing respiratory rate this will lead to dynamic hyperinflation, a major drive for dyspnea. Neutrophils are considered as an important inflammatory cell in COPD, which can be linked to the severity of the disease. However, macrophages also may play an important role in the lungs of patients with COPD. Macrophages can be recruited to the bronchiolar epithelium and release a number of inflammatory cytokines such as tumour necrosis factor (TNF-α) or produce elastolytic enzymes that eventually may contribute to the development of emphysema and the progression of the disease, which could possibly influence health status. Only part of health status could be explained by this type of airway inflammation. This indicates that a distinct pathological phenotype contributes to health status.

Few long-term studies reported effects of therapy on health status. In the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study health status was measured with the SGRQ during 3 years. Usage of ICS positively influenced health status in patients with moderate to severe COPD. In addition, the combination of ICS and a LABA can improve health status [16] where long-term tiotropium can slow down decline of health status [17]. Controversial effects in studies can be due to differences in population characteristics such as baseline exacerbation frequency or different drop-outs [14].
Our study showed that in our subgroups of patients with moderate to severe COPD long-term maintenance therapy with ICS improved SGRQ activity and CCQ total, symptom and functional scores, whereas stopping ICS worsened SGRQ total and activity score, and both CCQ total and symptom scores (Chapter 5). Adding a LABA to ICS improved improved short term CCQ total, symptoms and functional scores. However, during the subsequent 24 months, combination therapy did significantly worse on these outcomes compared with fluticasone alone. In conclusion, health status is an overall measure of impairment that is associated with a distinct inflammatory profile and can be influenced by long-term ICS therapy in subgroups of patients with COPD.
We observed positive effects on daily reported health status and lung function in patients with stable disease (Chapter 7). Long-term monitoring in combination with therapy in COPD has been shown to decrease the impact of exacerbations on health status, and decrease symptoms of exacerbations [18]. However, the number of patients with a minimal important difference was limited, which may hamper adherence to chronic medication in moderately severe COPD.

Chronic bronchitis

Despite the fact that 30% of patients with COPD have symptoms of chronic bronchitis, it is still controversial whether this points to a benign disorder or a relevant sub-phenotype. It is not yet clear how a normal lung changes into a lung where mucus production is exaggerated, contributing to obstruction of the upper and lower airways. Aiming at the underlying airway inflammation might be of therapeutic value. This is not an easy approach since the pathology in COPD is complex. It might be considered as a ‘burning process’ driven by inflammatory cells, pro-inflammatory cytokines and oxidative stress. The lungs react with an innate and adaptive response to clear this burning process. Inability to restrict this innate and adaptive immune response may contribute to remodelling, increasing mucous glands and mucus-producing cells in

the surface epithelium. Inflammatory mediators such as neutrophil elastase are important secretagogues for mucin producing cells. The exaggerated mucin production and defective clearance is responsible for the mucus hypersecretion and presence of chronic bronchitis.
In this thesis the presence of chronic bronchitis was associated with a distinct inflammatory cell profile in the airways, as measured in a large sample of induced sputum and bronchial biopsies (Chapter 4). Remarkably, patients with chronic bronchitis had significantly fewer eosinophils in biopsies and higher percentages of sputum eosinophils than COPD patients without these symptoms. This is suggestive of a preferential distribution of eosinophils towards the airway lumen in COPD patients with chronic bronchitis. In chapter 4 we conclude that the clinical symptoms of chronic bronchitis reflect a distinct sub-phenotype among patients with manifest COPD, as based on inflammatory cells in induced sputum and bronchial biopsies. This may be important when trying to tackle the underlying inflammation in order to reduce symptoms in patients. However, effects of treatment with ICS with or without salmeterol was not different between COPD patients with and without chronic bronchitis (Chapter 5) and the presence of chronic bronchitis was not a predictor of the effect of therapy on the accelerated decline in FEV_1 in our study (Chapter 6). Therefore, according to our data it is still controversial whether chronic bronchitis can be considered as a relevant phenotype within COPD.

Long-term therapy with inhaled fluticasone propionate, with and without salmeterol

It is well-known that ICS can suppress the inflammatory process effectively in asthma. A potential similar effect on airways inflammation in COPD was the reason to prescribe this therapy on great scale in these patients. However, the effects in large studies of COPD are much more modest than in asthma. Current guidelines recommend maintenance treatment with ICS only in patients with advanced disease and a history of recurrent exacerbations. However, two recent studies suggested that prolonged therapy with ICS and a long-acting $ß_2$-agonist can attenuate FEV_1 decline in COPD.
The results of our study show that long-term maintenance therapy with fluticasone improves the rate of FEV_1 decline in the steroid-naïve patients with moderate to severe COPD included in our study (Chapter 5). This is accompanied by sustained improvement of airway hyperresponsiveness and reduced dyspnoea. Adding salmeterol to fluticasone provides a sustained

improvement in FEV_1-level and dyspnoea, but does not further improve the rate of FEV_1 decline and slightly worsens health status.

Effects on clinical measurements

Previous studies showed initial improvement in FEV_1, but could not demonstrate benefit on the subsequent annual FEV_1 decline in COPD [19-22]. We did not find an initial improvement in FEV_1, yet we believe that we were able to detect longstanding improvements in FEV_1 decline due to differences in study design. The vast majority of our patients was completely steroid-naïve, whereas over 50% of patients used steroids in previous studies [16;21;23-25]. By choosing steroid-naïve patients, we aimed to avoid patients with unknown previous benefits by inhaled steroids at baseline, and to limit drop-outs on placebo treatment. Furthermore, we used relatively high inhaled steroid doses in patients with predominantly mild to moderate COPD, who were examined in only two centers in which we took great care to apply the same methodology. The observed improvements in airway hyperresponsiveness and dyspnoea corroborate results from a previous study, showing that ICS can reduce airway hyperresponsiveness and dyspnoea after 9 and 33 months [22]. Discontinuation of ICS led to relapse of these disease features in our study, extending previous findings where stopping ICS led to a prompt deterioration in FEV_1 [24] and corroborating that inclusion of steroid naive patients may have been a decisive contribution to the differential effect between ICS and placebo. In keeping with previous reports, addition of salmeterol to fluticasone provided a consistent improvement in the level of FEV_1, yet we could not show further modification of long-term decline in FEV_1 [16;23]. Short-term addition of salmeterol improved daily reported health status and peak expiratory flow, which reached minimal important differences. Therefore, patients may actually experience the benefits in daily life. This suggests that addition of a LABA to ICS can be provided in order to relieve instant symptoms, but does not affect disease progression.

Effects on inflammatory cell counts

Our study shows that 2.5-year maintenance therapy with ICS in COPD reduces bronchial T lymphocyte and mast cell numbers, whilst increasing the number of eosinophils and integrity of bronchial epithelium, which was accompanied by a reduction in sputum cell counts. Previous short-tem studies investigating COPD patients have shown different anti-inflammatory effects of ICS in COPD [26-28]. 2-Month treatment in a small sample of patients with COPD showed

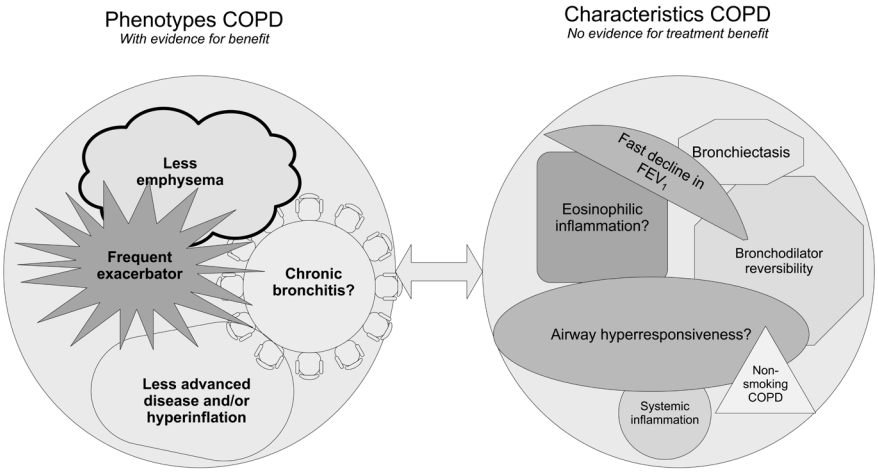
a reduction in sputum neutrophils and total cells by high dose budesonide in patients with moderate disease [29]. 3-Month treatment with the combination therapy of ICS and LABA reduced IL-8 and MMP-9, but did not statistically influence total number of cells in induced sputum compared with tiotropium in older patients with a FEV_1 around 55% of predicted and relatively poor quality of life (SGRQ total score of around 45) [30]. 3-Month treatment with ICS alone reduced subepithelial mast cells, but not CD8, CD68 or neutrophils in bronchial biopsies compared to placebo in 30 patients with an FEV_1 around 45% of predicted [31]. 13 Week treatment with the combination of 2 times daily 250/50 fluticasone and salmeterol reduced eosinophils in sputum and CD8, CD4, CD45 in bronchial biopsies, but not CD68 macrophages in 140 patients with moderate to severe COPD [32]. In addition, combination therapy reduced differential neutrophils and total eosinophils. This study did not include an ICS or LABA alone treatment group. 3-Month combination treatment with SFP (50/500, twice daily) suppressed $CD8^+$ T cells and CD68 macrophages in bronchial biopsies compared to placebo, but failed to find a result with fluticasone alone [33]. One possible explanation for the less clear effect of ICS on suppression of inflammation in COPD as compared to asthma may be the reduced expression of the enzyme histone deacetylase-2, which is required by ICS to switch off activated inflammatory genes in more advanced disease [34]. However, our study showed that beneficial effects in subgroups of patients with more moderate disease can be maintained during long-term treatment up to 30 months. Interestingly, the positive findings on inflammatory effects are consistent with positive effects on lung function decline and symptoms, which points towards a clinically relevant treatment benefit.

Who will benefit? Towards clinical phenotyping

In this thesis, the most important clinical question to be answered is who will benefit from ICS with or without LABA. The patient with COPD sitting in front of you when being a GP or pulmonologist is bothered by his or her symptoms and doctor and patient have to jointly decide whether to start with therapy. This is not an easy question and this thesis may add a small piece to the puzzle. Clinical phenotyping focuses on differences between individuals with COPD with regard to the effects of therapy on outcome. Figure 1 shows an example of visualising clinical phenotypes according to treatment effects. This is a dynamic model where, based on new evidence, phenotypes can switch between the left and right circle. This figure does not contain information on clinical phenotypes with an effect on clinical outcome, because we focused on

the effects of therapy, as it is important for daily practice.

Figure 1. Clinical phenotypes in COPD: a dynamic model



Chapter 6 shows that in our subgroup of patients with COPD, patients who had fewer packyears smoked, preserved diffusion capacity of the lung, limited hyperinflation, and lower number of total cells in induced sputum benefited most from inhaled corticosteroids. In addition, a higher number of total cells and neutrophils in induced sputum predicted a more effective reduction of the number of $CD3^+$ in bronchial biopsies by treatment with fluticasone at 30 months. This may suggest that earlier stages of the disease or a subtype of COPD patients in whom airway obstruction is accompanied with less severe emphysema predict a better course of lung function with treatment of ICS in patients with moderate to severe COPD. This extends findings from Lee *et al*, showing that short-term treatment response to ICS was smaller in patients with an emphysyma-dominant phenotype compared to the obstruction-dominant phenotype and moderate to severe COPD [35].

The severity in COPD is currently based on the level of FEV_1, symptoms and future risk of exacerbations [1]. However, it is the question whether to focus solely on these features [36]. In additon, it unclear whether early stages of disease should be treated or should we wait till there is more advanced disease? COPD is a disease with early (small) airway narrowing with continuos presence of inflammation where later in advanced disease tissue repair contributes to airway remodeling including irreversibe fibrosis [37]. Results from the Trial of Inhaled Steroids and Long-acting $ß_2$-agonists (TRISTAN) study showed that clinical benefits were not restricted to more advanced

disease as based on the level of FEV_1 and it is important also to focus on more mild disease where is much more to gain [38]. In our study, patients with less emphysema benefited more from ICS. The ECLIPSE study showed that emphysema as assessed with CT was associated with more rapid decline in FEV_1 in patients with more severe disease (FEV_1 48% of predicted) [39]. In a recent study 279 patients with COPD (GOLD stage I:26%, II:45%, III:24%, IV:5%) were followed for five years [40]. Emphysema severity as measured by either $\%K_{CO}$ of CT scan was independently associated with a rapid decline in FEV_1. This supports our findings that a clinical phenotype defined by emphysema should be considered in clinical trials with COPD or in daily practice, given its possible consequences for therapy.

Patients with asthma are more sensitive to the anti-inflammatory actions of corticosteroids than patients with COPD. Interestingly, in COPD several characteristics associated with asthma, such as bronchodilator responsiveness, airway hyperresponsiveness and eosinophilic inflammation have been reported to predict beneficial effects of ICS. However, in our study patients with asthma were carefullly excluded by doctor's diagnosis and self-reported symptoms, treatment or diagnosis of asthma. It is interesting whether the presence of asthmatic characteristics in COPD could point to a specific phenotype. Previous studies showed more benefit in COPD patients with more bronchodilator responsiveness [41-43]. However, these results have not been confirmed by others [21]. In 32 patients with mild to moderate COPD, manitol hyperresponsiveness was significantly associated with eosinophil numbers and soluble markers in sputum [44]. Because of the high specificity and low sensitivity this suggests that mannitol hyperresponsiveness can be used as a guidance for individualised treatment. However, this has to be confirmed in clinical trials. Reversibility in our study was not a predictor of clinical outcome and suggests that the underlying mechanisms contributing to reversibility in COPD may be different from reversibility in asthma. A previous study did not find improvement in FEV_1 after 6 weeks of treatment with ICS of patients with COPD who where hyperresponsive to adenosine 5'-monophosphate, which is an indirect stimulus [45]. We extended these findings by showing that airway hyperresponsiveness was no predictor of the long-term beneficial effects of ICS. Sputum eosinophils have been predictive of a larger increase of FEV_1, health status and exacerbations in studies with a duration up to one year. 82 patients with severe COPD (FEV_1 around 38% of predicted) were treated according to their symptoms or to both symptoms and eosinphilic inflammation. Intriguingly, guidance by eosinophilic inflammation led to a reduction in the

frequency of hospital admissions [46]. In our subgroup of patients we did not find such effect with maintenance therapy with ICS for 2.5 years. Rather than specific characteristics of asthma our data point to the direction that in certain subgroups of COPD such as patients with less advanced disease or a subphenotype with less emphysema, ICS may be beneficial. This may aid in the process of unraveling wich clinical phenotypes are important in COPD (Figure 1). Current guidelines advise long-term treatment only in patients with advanced disease and frequent exacerbations. External validation of our results in larger subsets of patients with moderate to severe COPD is necessary to be able to generalise our results into daily practice. This would allow extending current recommendations in COPD guidelines by offering a more optimistic perspective for subgroups of patients with COPD.

Limitations

We believe that the strength of our study is that it was designed to investigate the potential benefits of continuation of inhaled corticosteroids, with and without long-acting $ß_2$-agonists, in patients with stable, moderate to severe COPD who in the vast majority had not been treated with these drugs in the past. We examined long-term treatment and its discontinuation in the same study, including a placebo-arm. It has been shown that discontinuation of previously prescribed ICS in COPD leads to increased exacerbation rate [23], which may have increased the number of drop-outs in the placebo-groups of other studies. By including steroid-naïve patients in the present study, such selective drop-out was avoided, and this may explain the significant benefits of ICS on lung function decline as observed in the present study.

Still, some limitations apply to our study. For clinical endpoints, the number of patients was relatively low due to our primary aim to examine bronchial inflammation. This is the likely explanation for observing only small effects on health status. In addition, due to practical reasons, we did not include a 5th arm investigating salmeterol alone, but based on previous studies it can be anticipated that salmeterol has no disease modifying effect by itself [25;47]. This was an efficacy trial. Therefore, only data from patients using more than 70% of the prescribed dose were analysed. This may have underestimated the (detrimental) treatment effects in the placebo group due to expected drop-outs in this group. The sample size of our study was too small to investigate adverse events. Several studies reported a higher probability of having pneumonia as an adverse event among patients using ICS. The TORCH trial reported a higher risk on pneumonia with long-term fluticasone [48]. This

was supported by an updated meta-analysis showing a significant increased risk on pneumonia with ICS (RR 1.57, 95% CI1.41-1.75) [49]. It could be that usage of ICS leads to local immunosuppressive effects inducing an increased susceptibility to infections, especially in patients with more advanced disease. A detailed profile of the underlying inflammatory pathology is difficult to obtain. Pathological changes in COPD appear in central and peripheral airways and in the parenchyma, whereas in the lungs of smokers the inflammatory cells are not uniformly distributed [50]. The small airways play an important role in the pathogenesis of COPD [51] and by using bronchial biopsies of the larger airways and induced sputum, we focused only on the central airways.

Conclusion

Many COPD studies performed in the past were large epidemiological trials directed at clinical data or specifically directed at the inflammatory process in small samples with a small duration. However, the patient with COPD in front of the doctor experiences symptoms as a result of the complex pathogenesis of the disease. Physicians are trained to look at the patient as a whole. This should include understanding the patient and his disease perception, the symptoms and limitations belonging to the disease, but also the underlying components of the multiple pathways leading to progression of the disease [52]. Besides impairment in lung function other factors such as hyperinflation, emphysema, cough and sputum, and persistent inflammation should be evaluated, also in patients with less advanced COPD. Only then, we can put a step forward towards clinical phenotyping directed at individualised therapy [53]. The unique setting of the GLUCOLD study has provided the cooperation between multiple departments resulting in detailed phenotyping of patients with predominantly moderate COPD, including clinical as well as inflammatory data from induced sputum and bronchial biopsies. By showing that certain subgroups of COPD such as patients with less advanced disease or a subphenotype with less emphysema can benefit from inhaled corticosteroids, our results may offer an indication for a promising perspective for subgroups of patients with COPD towards the potential of slowing down the progression of the disease in the future.

Current implications in daily practice

Patient-centred care is the solution for improvement of quality of care and costs for chronic disease. Primary care may provide a setting where patient-centred care can be implemented. GPs can deliver integrated care with

other health care providers. Continuity of nearby presence of care can help the patient with integrating personal goals in daily life. So, how can we build bridges between evidence based medicine and practical daily care. It is increasingly known that diagnoses such as COPD are strongly related to other chronic diseases such as cardiovascular disease [54] and in the future we may go beyond specific diagnoses towards fingerprints of inflammation and/or RNA/DNA. However, we are not there yet and have to take one step at a time. Interpreting current guidelines is difficult since many patients with COPD have been and still are excluded from large randomised controlled trials [55]. So how can we start with implementing current knowledge in daily care? Is it sufficient to treat patients ad hoc? Do we rely on symptoms, exacerbations and FEV_1 or should we pro-actively focus on clinical phenotyping, including extended assessment in early disease? With increasing costs in society in the nearby future, the latter may be difficult to obtain with the enormous amount of patients with asthma and COPD. More simply, we cannot measure everything in every patient at any moment. It will be an enormous challenge to examine which patients with mild or more advanced disease will need early extended assessment in order to improve care (and reduce costs in the end).

The authors' perspective

How can we implement current evidence into daily practice? At this moment, I work as a general practitioner in a large primary care practice in The Hague. Around 1,000 patients (from a total of 10,500 registered persons) have a diagnosis of asthma and/or COPD. Together with lung physicians, we have started implementing integrated care. The novelty in our project is that caretakers from first and secondary care communicate in a structured and efficient way, in order to decide which patient needs further assessment using innovative e-health instruments. With current political movements in the Netherlands, the future will show whether programs like this will be stimulated, facilitated or stopped by the government. For now, a specialised lung nurse will make a detailed assessment of the patients' disease using questionnaires and spirometry within the primary care practice. Teleconsultation will be used to improve communication and feedback between primary and secondary care. If necessary, patients will have a secondary assessment in the hospital, with the intention of returning to primary care within 3 months of time. Few patients will actually be referred to a hospital. In addition, patient-centered care will be enhanced by usage of an internet based self-management programme, www.PatientCoach.nl. This programme was developed in Leiden for patients with

chronic disease and provides the possibility to optimise disease management, including the possibility of communication between the patient and the caretaker as well as scientific evaluation. Registration with the programme is integrated in the electronic registration system of the primary care physician. Currently, we are performing an implementation study with PatientCoach for patients with moderate asthma in primary care (IMPlementation strategies of internet-based Asthma Self-management Support in usual carE (IMPASSE) Trial). Patients with asthma can monitor their asthma symptoms and lung function at home with a consequent medication advice according to an algorithm based on current guidelines. In addition, we have started the Pulmonary Rehabilitation of Asthma and COPD: a Trial of sustained Internet-based Self-management Support (PRACTISS) study. The aim of this study is to assess the cost-effectiveness of sustaining self-management support via PatientCoach as compared to usual care in patients with 1) severe asthma who have completed pulmonary rehabilitation in Davos and 2) COPD patients who have completed pulmonary rehabilitation in the Rijnlands Rehabilitation Centre in The Netherlands.

The simplest reason for taking all of these efforts is to improve chronic care and reduce the enormous distress that patients experience from their chronic disease, accompanied with a decrease in costs. By structuring basic daily care we may try to find a way not just to measure everything in every one, but to focus on clinical phenotyping, setting personal goals and individualised care. By performing research with new topics such as biomarkers or e-health and integrating primary and secondary care, patients may benefit. This may lead eventually towards integrated disease management, individualised care, improved quality of life, and possibly slowing down the progression of chronic disease.

Abbreviations

α1AT	Alpha-1 Antitrypsin
BAL	Bronchoalveolar Lavage
Body box	Plethysmography
CCQ	Clinical COPD Questionnaire
Chest X-ray	Chest radiograph
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECLIPSE	Evaluation of COPD Longitudinally to Identify Surrogate Endpoints
FEV_1	Forced Expiratory Volume in one second
FIV_1	Forced Inspiratory Volume in one second
GM-CSF	Colony-Stimulating Factor
GLUCOLD	Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease study
GOLD guidelines	Global Initiative for COPD guidelines
Hb	Hemoglobine
ICS	Inhaled Corticosteroids
IgE	Immunoglobuline
IL-8	Interleukin (IL)-8
IMPASSE	IMPlementation strategies of internet-based Asthma Self-management Support in usual carE trial
ISOLDE	Inhaled Steroids in Obstructive Lung Disease
K_{CO}	transfer factor for carbon-monoxide
LABA	Long-Acting $ß_2$-Agonist
LTB_4	Leukotriene B_4

LUMC	Leiden University Medical Center
MMPs	Matrix Metalloproteinases
6 MWD	6-Minute Walk test
NWO	Netherlands Organization for Scientific Research
N2 sb test	single-breath nitrogen test
PEF	Peak Expiratory Flow
PC_{20} methacholine	the provocative concentration of methacholine that causes a decrease in FEV_1 of 20%
PRACTISS	Pulmonary Rehabilitation of Asthma and COPD: a Trial of sustained Internet-based Self-management Support study
TNF-α	Tumor Necrosis Factor-α
TGF-ß	Transforming Growth Factor
QOL-RIQ	Quality of Life for Respiratory Illness Questionnaire
Rand36	Short Form Health Survey
RNA	Ribonucleic Acid
SAB	Stichting Astma Bestrijding
SGRQ	St. George Respiratory Questionnaire study
SLPI	Leucocyte Protease Inhibitor
TIMPs	Tissue Inhibitor of Metalloproteinases
TRISTAN	Trial of Inhaled Steroids and Long-acting $ß_2$-agonists study
TORCH	Towards a Revolution in COPD Health study
UMCG	University Medical Center Groningen
VAS	Visual Analogue Scale
TLC	Total Lung Capacity
CO-diffusion capacity	Carbon-monoxide-diffusion capacity

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