

REVIEW

Do small airway abnormalities characterize asthma phenotypes? In search of proof

M. Contoli¹, M. Kraft², Q. Hamid³, J. Bousquet⁴, K. F. Rabe⁵, L. M. Fabbri⁶ and A. Papi¹

¹Research Centre on Asthma and COPD, Department of Clinical and Experimental Medicine, University of Ferrara, Ferrara, Italy, ²Department of Medicine, Duke University Medical Center, Durham, NC, USA, ³Meakins-Christie Laboratories, McGill University, Montreal, Québec, Canada, ⁴Department of Respiratory Medicine, Montpellier University, Montpellier, France, ⁵Hospital Grosshansdorf, Center for Pneumology and Thoracic Surgery, Woehrendamm, Grosshansdorf, Germany and ⁶Department of Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy

Clinical & Experimental Allergy

Correspondence:

Marco Contoli, Research Centre on Asthma and COPD, Department of Clinical and Experimental Medicine, University of Ferrara, 44121, Ferrara, Italy.

E-mail: ctm@unife.it

Cite this as: M. Contoli, M. Kraft, Q. Hamid, J. Bousquet, K. F. Rabe, L. M. Fabbri, A. Papi, *Clinical & Experimental Allergy*, 2012 (42) 1150–1160.

Summary

The role of small airway abnormalities in asthma pathogenesis has been extensively studied and debated for several decades. However, whether or not small airway abnormalities play a relevant role in specific phenotypes of asthmatic patients and contribute to clinical presentation is largely unknown. In the present review, we evaluated available data on the role of small airways in severe asthma, with a further focus on asthma in smokers and asthma in the elderly. These phenotypes are characterized by a poor response to treatment and they can represent a model of greater small airway impairment. In severe asthmatics, small airway involvement has been shown through evidence of both distal inflammation and of increased air trapping. The few available data on asthmatics who smoke, and elderly asthmatics, similarly suggests that small airway abnormalities contribute to the pathogenesis of the disease. In this perspective, there could be a rationale for specifically assessing small airway impairment in these patients and for clinical studies evaluating whether pharmacological approaches targeting the more peripheral airways result in clinical benefits beyond conventional therapy.

Keywords asthma, small airways, phenotypes, inflammation

Submitted 25 October 2011; revised 11 January 2012; accepted 18 January 2012

Introduction

Asthma is a heterogeneous disease resulting from the complex interaction between genetic and environmental factors leading to a chronic inflammation of the whole bronchial tree from central to peripheral airways [1]. The pathophysiology of small airways (i.e. the more peripheral airways characterized by an internal diameter less than 2 mm) and the putative role of their abnormalities in asthma pathogenesis have been extensively debated in the last few decades [2–6]. However, despite the many reviews addressing this issue, the original data are limited mainly due to the relative inaccessibility of small airways and to the lack of a unanimously accepted gold standard to measure their abnormalities. Postma et al. recently reviewed 19 studies in which small airway abnormalities were directly explored by means of surgical/autoptic samples or transbronchial biopsies [6]. Among these studies, 10 refer to patients who died of asthma attacks [7–16],

whereas virtually all the remaining studies include patients with severe asthma [17–23].

Therefore, the knowledge on small airways in asthma is still incomplete and mainly focused upon more severe disease. Nevertheless, the small airways represent a preferred topic of discussion in the current literature on asthma. Indeed, in the last 3 years, more than 150 articles have been published on this issue, including both original studies, but mainly viewpoints and reviews. This trend testifies to a keen interest on the involvement of small airways in asthma pathophysiology and clinical expression, which requires additional data rather than review and interpretation.

In the last years, it has become clear that phenotyping is the cornerstone to interpret the clinical and pathological diversity of asthma that can lead to individualized treatment for each single phenotype or patient. A disease phenotype is defined as the visible characteristic of the disease resulting from the interaction between the underlying genetic substrate and the

environment. A phenotype should be able to classify patients into distinct subgroups that provide prognostic information and allow us to better determine appropriate therapy that alters clinically meaningful outcomes. Hence, the ultimate goal of phenotyping in medicine is to allow the identification of patient groups with unique prognostic or therapeutic characteristics [24]. Several approaches have been used to phenotype asthma based on: i) airway immunoinflammatory profile (e.g. eosinophilic vs. non-eosinophilic or paucigranulocytic asthma); ii) trigger factors (e.g. allergen-, occupational-, exercise- or aspirin-induced asthma) and iii) clinical presentation, particularly disease severity and response to treatment (e.g. severe asthma, exacerbate-prone asthma, asthma with fixed airflow obstruction, treatment-resistant asthma) [25]. The specific impact of small airway abnormalities on selected asthma phenotypes, and the identification of specific 'small airway asthma phenotypes' have never been considered. The issue is whether the small airway impairment is a feature common to all asthma phenotypes or if it selectively drives the clinical expression of a specific subgroup of patients. The variable involvement of small airways could be a contributor to explain the heterogeneity of the data available on small airways in asthma. Furthermore, small airway's contribution could explain the lack of efficacy of certain inhaled therapies that do not target this compartment. Indeed, in some asthma phenotypes commonly linked by poor response to treatment, small airway impairment might play a particularly relevant role.

In this perspective, we consider the involvement of small airways within the broad definition of severe asthma, which includes the so-called 'difficult-to-treat' or treatment-refractory patients [26]. Among these patients, we particularly focused upon elderly asthmatic patients (and particularly those with a long history of disease and/or with fixed airflow obstruction) and smoking asthmatics. We discuss the latter group separately because they represent a group of understudied patients, as they are excluded from the vast majority of clinical trials yet deserve further medical and research attention to understand possible pathophysiological mechanisms linked to poor response to therapy.

Small airways in asthma

Pathology of small airways. Evidence in asthma

Airway inflammation and airway remodelling, i.e. sub-epithelial fibrosis associated with hypertrophy and hyperplasia of smooth muscle, are key features of asthma pathology [1]. Inflammation and remodelling also occur in the peripheral airways [18, 19, 21, 23, 27, 28] as documented in lung specimens or transbronchial biopsies from severe asthmatic patients or patients who

died of asthma. Ethical concerns have limited the extensive use of these invasive techniques to explore small airway abnormalities in asthma, particularly in mild asthma. To overcome such limitations more sophisticated techniques have been developed to indirectly assess small airway pathology.

Peripheral airway inflammation can be indirectly examined by measuring nitric oxide (NO) concentrations in single breath exhaled air at different flow rates [29, 30]. With this technique, using a mathematical model, it is possible to discriminate between the bronchial and alveolar NO levels, and therefore to indirectly evaluate peripheral airway inflammation. Alveolar NO has been related to markers of peripheral airway inflammation such as eosinophil cationic protein levels and eosinophil counts in bronchoalveolar lavage (BAL) of children [31] and adults [32] with asthma respectively. The source of alveolar NO is largely unknown. A recent *Ex vivo* study suggested the capability of peripheral airway bronchial epithelial cells to release NO when stimulated with several pro-inflammatory cytokines (including IL-1 β , TNF α , IFN- γ and IL-13) [33]. Moreover, higher levels of alveolar NO have been reported in severe asthmatic patients compared with mild to moderate patients [34, 35], suggesting a correlation between disease severity and the magnitude of small airway inflammation. However, a recent multi-centre study enrolling 200 non-smoking asthmatic patients (both children and adult), failed to document any association between alveolar NO levels and indexes of asthma control or severity [36].

Sequential sputum induction has been also proposed as indirect tool to assess the inflammation that occurs in the more peripheral compartment of the airways by the analysis of the samples collected in the late phase after the induction [37, 38]. Through this technique, Taha and Colleagues [39] documented increased numbers of eosinophils and Th-2 type cytokine positive cells, whereas Richer and Colleagues [38] found a significant reduction in neutrophils and no difference in eosinophils, in the later sputum samplings compared to earlier sputum samplings. Unfortunately, the inflammatory pattern of the small airways corresponding to the findings provided by these indirect methods have not been established, thus the precise anatomical compartment from which inflammatory biomarkers originate is not clearly defined. Moreover, and more generally, other limitations of these methodologies relate to the lack of reproducibility and standardisation.

Pathophysiology of asthma. Assessment of small airways

Although the small airways have very little impact on airflow resistance in normal conditions, there is evidence that their abnormalities significantly contrib-

ute to increasing airflow resistance in asthmatic patients, as documented via invasive endobronchial catheterization [40]. These studies were conducted mainly in mild asthmatic patients compared with healthy controls whereas only one study directly assessed and compared peripheral airflow resistance in asthmatic patients with or without concomitant airflow obstruction [41]. The study showed that the more severe the airflow obstruction the higher the contribution of peripheral airflow resistance to total airflow obstruction. However, the contribution of small airway abnormalities in different stages or phenotypes of the disease has not been thoroughly explored.

From a functional point of view, small airway abnormalities lead to peripheral heterogeneity of the ventilation and to premature airway closure and air trapping. Functional tests have been used to indirectly assess these abnormalities. In particular, it has been documented that in asthma residual volume (RV) correlates with both peripheral airway resistances (directly assessed by endobronchial catheterization) [20] and parameters of air trapping evaluated by high resolution CT scan [42]. Thus, increased RV, and more precisely RV over total lung capacity (RV/TLC) ratio above the upper limit of normal obtained from a reference equation, is considered a valid surrogate of air trapping. In addition, forced vital capacity (FVC) has been shown to correlate inversely with RV/TLC [43], indicating that reduction in FVC can be considered a marker of air trapping that must be complemented with lung volume measurements. The single breath nitrogen washout test can measure peripheral ventilatory inhomogeneity (slope of phase III) and airway closure (closing capacity) and thus it represents another functional test that has been extensively used to indirectly measure small airway functional abnormalities in asthmatic patients.

Imaging has more recently moved into the assessment of small airways in obstructive pulmonary diseases. Computed tomography (CT) scan of the chest, even at high resolution, allows direct assessment only of large and medium airways (diameter 2–2.5 mm). However, recently developed software applications capable of analysing lung parenchyma scans, could provide indirect information (both qualitative and quantitative) of small airway impairment. Areas of mosaic lung attenuation on inspiratory high resolution CT scan (indirect signs of ventilatory inhomogeneity) and on expiratory scan (signs of air trapping) have been studied as markers of small airway disease [44, 45]. Interestingly, imaging could be considered a tool able to link small airway pathology, function and clinical presentation. Indeed, it has been found that CT-estimated air trapping correlates with both classical lung function parameters of air trapping [42], premature airway closure and with disease severity [46].

These novel tools could provide additional pieces of information on the relative contribution of small airway abnormalities in the severity of asthma presentation and/or asthma phenotypes.

Small airway abnormalities in severe asthma

Severe asthma accounts for only 5–10% of patients with asthma; however, it is responsible for a considerable portion of the health care costs associated with this disease [26, 47–49]. One of the main problems has been the lack of a unique and unanimously accepted definition of severe asthma for many years. Thus, several faces of asthma severity, quite often overlapping one another, have been investigated and described. One of the most comprehensive approach recently proposed to define severe asthma proposed the term 'severe refractory asthma' only for those "asthmatic patients in whom alternative diagnoses have been excluded, comorbidities have been treated, trigger factors have been removed (if possible) and compliance with treatment has been checked, but still have poor asthma control or frequent (>2) severe exacerbations per year, despite the prescription of high-intensity treatment or can only maintain adequate control when taking systemic corticosteroids, and are thereby at risk of serious adverse effects of treatment [47]".

Operatively, a World Health Organisation (WHO) statement defined severe asthma as "uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced growth in children)" [26]. Therefore, based on this latter definition, the phenotype of severe asthma includes: i) patients severely ill, not properly treated, or not treated at all; ii) patients that are 'difficult to treat' because of the presence of concomitant factors that jeopardise the efficacy of treatment (poor adherence to treatment, comorbidities, smoking habit); iii) patients that are refractory to appropriate treatment even at highest doses and do not reach proper control (uncontrolled patients, patients developing fixed airflow obstruction, exacerbation-prone patients).

Recently, several studies have been performed to characterize various aspects of severe asthma. Only few of them have directly focused on the assessment of small airways providing some relevant pieces of information.

Pathology

Intense inflammation, luminal plugging and airway structural abnormalities have been demonstrated in post-mortem tissue of peripheral airways from patients

who died from severe exacerbation [28, 50–52], i.e. the most severe and acute clinical presentation of asthma. In these cases, it could not be clarified whether the magnitude of the small airway abnormalities reflected the severity of the acute phase or whether it was related to the severity of the underlying disease. Important hints on small airway abnormalities in severe asthma have been obtained in living subjects via transbronchial biopsies or in surgical specimens of asthmatic patients undergoing lung resection. These studies showed higher number of inflammatory cells [53] and a significantly increased percentage of mast cells in small vs. large airways [17]. Only one study compared the characteristics of small airway inflammation in severe vs. moderate asthmatic patients through transbronchial biopsies, and showed more pronounced neutrophilic inflammation [23] in the small airways of severe compared with moderate asthmatics (Fig. 1a). Moreover, an interesting comparison comes from a study involving a specific sub-phenotype of severe difficult-to-control asthma i.e. nocturnal asthma. In transbronchial biopsies, Kraft and colleagues found that the number of inflammatory cells was significantly higher in the distal airways of patients with nocturnal asthma compared with non-nocturnal, controlled asthmatic patients [20]. Indirect parameters of peripheral airway inflammation, such as alveolar NO, were found elevated in patients with uncontrolled asthma despite regular treatment compared with mild-to-moderate controlled asthmatic patients and normal controls [32]. Similarly, alveolar NO was higher in patients with steroid-dependent asthma compared with non-steroid-dependent asthmatic patients [35].

Taken together, these data indicate that a more severe, but also a qualitatively different inflammation, occurs in the airways of severe asthmatic patients compared to moderate or controlled asthmatic patients. Alternatively, inflammation occurs throughout the lung in asthma, and this process is present in severe asthma.

Function

Recent studies have used different approaches to characterize severe asthma and/or assess sub-phenotypes of severe asthma [54–57]. The results of these studies provided some relevant hints on the involvement of small airway in severe asthma. Of particular interest are the findings of the Severe Asthma Research Network (SARP) [56], where an unsupervised cluster analysis was performed to identify particular characteristics associated with severe asthma. [58]. The study showed that severe asthmatic patients had prominent air trapping (detected as increased RV/TLC ratio) over the entire range of airflow obstruction severity and that non-severe asthmatic patients did not exhibit significant air trapping even at the more severe stages of airflow obstruction expressed as FEV₁/FVC ratio [43]. Thus, severity of asthma appeared to be linked to enhanced air trapping rather than to the level of airflow obstruction. Similarly, the European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) study [57], a cross-sectional observational study comparing severe asthma with mild-to-moderate asthma, found that RV increased (paralleled by a reduction in forced vital capacity - FVC) in severe asthmatic patients as compared with controls (Fig. 1b).

Additional studies have evaluated functional parameters of small airway abnormalities in relation to asthma severity/control. Using the single-breath nitrogen washout test, In't Veen and colleagues found that increased closing volume (CV) and closing capacity (CC) were the only pulmonary function variables that discriminated between patients with difficult-to-control asthma (i.e. experiencing frequent exacerbations despite regular and maximal inhalation treatment) and patients with stable asthma [59]. In a cross-sectional study, Bourdin et al. suggested an association between increase in the phase III slope (dN₂) of the washout curve and poor asthma

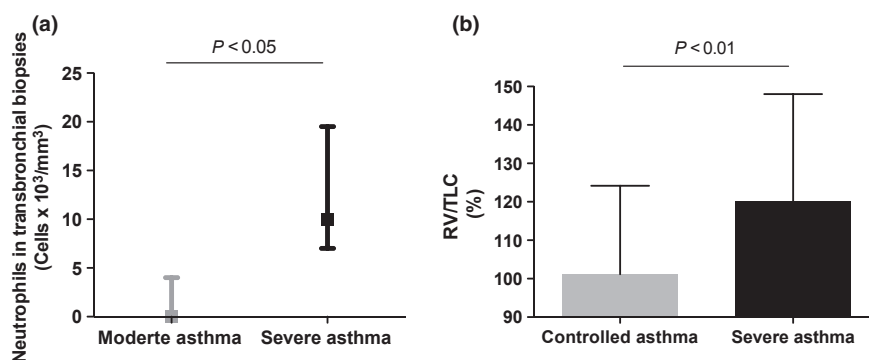


Fig. 1. Small airways abnormalities in severe asthmatic patients. (a) Transbronchial biopsies document increased neutrophilic inflammation in small airways of severe compared with moderate asthmatic patients (data obtained from [23]). (b) Functional parameters of enhanced airtrapping/hyperinflation (RV/TLC ratio) are recorded in severe compared with milder asthmatic patients (data obtained from [57]). (RV, residual volume; TLC, total lung capacity).

control, high exacerbation rate and the need for a high daily dose of inhaled corticosteroids in a cohort of asthmatic patients with normal FEV₁ [60]. Longitudinal studies are needed to further explore this observation. Moreover, a recent study showed a correlation between functional parameters of air trapping (including increased RV) and of heterogeneity of peripheral airway ventilation and closure (including increased dN₂, and CC) with levels of alveolar NO in severe asthmatic patients, but not in mild-moderate controlled patients [35], supporting that in lung periphery airway inflammation and functional abnormalities are inter-related and positively associated with asthma severity.

Finally, impulse oscillometry (IOS) is an objective and non-invasive measurement of lung function that has the potential to examine independently both small- and large-airway airflow resistance [61]. A very recent study showed higher values of small airway (but not of central airway) resistance in children with uncontrolled asthma compared with controlled patients [62].

Taken together, these data indicate that diverse pathological events occur in the peripheral airways of severe vs. mild-to-moderate asthmatic patients leading to premature airway closure and peripheral air trapping in the more severe patients.

Small airway abnormalities in elderly asthmatic patients with long history of asthma and/or with fixed airflow obstruction.

Asthma in the elderly has been only minimally studied. Virtually all the published studies, particularly randomized controlled studies, recruited young asthmatics and excluded subjects over 65 years of age to avoid the inclusion of subjects with other obstructive lung disorders such as chronic obstructive pulmonary disease (COPD). Nonetheless, it is estimated that 7–9% of individuals over the age of 70 have asthma [63].

Diagnosis and management of asthma in the elderly population is still an open challenge. Despite the success of asthma treatment in younger adults and children both in terms of decreased mortality and of increased quality of life, disease management in the older population remains an unmet medical need [63]. Treatment and control of asthma in the elderly is often less effective than in younger asthmatics. Several factors have been claimed such as poor perception of symptoms, impaired inhaler technique and poor adherence to treatment [63, 64]. Whether poor response to treatment in elderly asthmatic patients can be also linked to prominent small airway abnormalities has never been specifically addressed.

Lung function physiologically declines with ageing; there is also evidence that lung function decline in asthmatic patients occurs more rapidly than in the

healthy population and the rate of decline is greater in elderly asthmatics as compared with younger patients [65]. Moreover, several studies document that elderly patients are more likely to experience incomplete reversible airflow obstruction [66–68] leading to the development of fixed airflow obstruction. Therefore, it appears that ageing and asthma interact in promoting worsening of lung function.

During the course of ageing, a proportion of the elastic fibres in the peripheral airways degenerate [69, 70], and supporting tissues around the airways are progressively lost. These aging-related physiological changes could contribute to increased air trapping, small airway collapsibility and premature small airway closure. On the other hand, the consequences of disease duration on small airway abnormalities have been highlighted in a recent study evaluating lung function in two groups of age-matched elderly asthmatic patients with a shorter or a longer duration of asthma [67]. Elderly asthmatic patients with longer duration of the disease had higher functional signs of air trapping (e.g. increased RV/TLC ratio) [67] (Fig. 2a). Taking increased RV as a sign of peripheral airway abnormalities, the study suggests that small airway abnormalities worsen progressively over time in asthmatic patients supporting an interaction between ageing and duration of the disease in promoting small airway abnormalities.

Whether small airway impairment also contributes to the development of fixed airflow obstruction or whether asthmatic patients with fixed airflow obstruction have more intense small airway abnormalities are still open questions. Indeed, the reasons for the development of incompletely reversible airflow obstruction, despite being classically linked to airway remodelling due to long-standing chronic airway inflammation [71], is largely unknown. The development of a fixed airflow obstruction in elderly asthmatic patients is a crucial issue because it raises important concerns – especially in this population – of differential diagnosis between asthma and COPD. A study published some years ago evaluated aged matched elderly asthmatic and COPD patients sharing a similar functional presentation, i.e. a similar fixed airflow obstruction [72]. The study found that, despite the two groups of patients were indistinguishable from the functional point of view (fixed airflow obstruction), they were significantly different in terms of airway inflammation (enhanced eosinophilic inflammation and airway remodelling in patients with a history of asthma) and of other functional parameters reflecting peripheral airway abnormalities (increased RV and impaired diffusion capacity in patients with COPD). The 5-year follow-up showed that asthmatic patients with fixed airflow obstruction experience a faster lung function decline compared with asthmatic patients with fully reversible airflow obstruction [73]. Moreover,

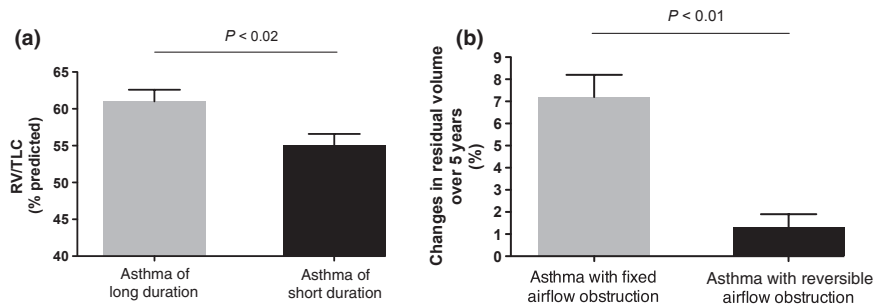


Fig. 2. Small airway abnormalities in elderly asthmatic patients with long history of asthma and/or with fixed airflow obstruction. (a) The degree of hyperinflation is significantly greater in the elderly asthmatic patients with longer disease duration compared with patients with shorter disease duration (data obtained from [67]). (b) Asthmatic patients with fixed airflow obstruction experience significant increase in airtrapping over time compared with patients with fully reversible airflow obstruction suggesting a prominent small airway impairment (data obtained from [73]).

accelerated lung function decline was paralleled by an increase in RV over time in asthmatic patients with fixed airflow obstruction, but not in asthmatic patients with fully reversible airflow obstruction (Fig. 2b). Hence, the study suggests interplay between the development of fixed airflow obstruction and the progression of small airway abnormalities.

No study has so far specifically evaluated small pathology in these clinical conditions.

Small airway abnormalities in smoking asthmatic patients

Up to 30% of asthmatic patients smoke, a smoking rate that is similar to the general population [74]. Despite the significant proportion of smoking asthmatic patients and the recognized negative effects of smoking on asthma, the underlying pathological processes of smoke-induced deterioration of asthma have not been thoroughly investigated. Moreover, very few data are available for specific management of smoking asthmatic patients mainly because these patients are excluded from large pharmacological clinical trials and only small sized studies have addressed this issue.

Tobacco smoking negatively affects the natural history of asthma and in particular, it negatively impacts on clinical outcomes and response to treatment. Indeed, smoker asthmatic patients experience faster lung function decline [65], increased frequency of exacerbations [75] and reduced asthma control [75, 76]. Impaired sensitivity to both inhaled and systemic corticosteroids has been reported in asthmatic patients who smoke. Indeed, it has been shown that treatment with inhaled corticosteroids (high doses of fluticasone, 1000 mcg/daily) is virtually ineffective in improving lung function in steroid naïve mild asthmatic patients who smoke, whereas in asthmatic patients who do not smoke the improvement is substantial [77]. Similarly, 2-week treatment with 40 mg daily of oral prednisolone did not improve FEV₁ in a group of smoker asthmatic patients, whereas

it resulted in a significant improvement in never-smoker asthmatic patients [78]. It has also been reported that impaired corticosteroid sensitivity in asthmatic patients who smoke can at least in part be overcome by increasing the dose of inhaled corticosteroids [79]. Moreover, preliminary studies reported that 8 weeks of leukotriene-receptor antagonist treatment, but not inhaled beclomethasone, resulted in significant improvement in peak expiratory flow (PEF) in asthmatic patients who smoke [80] and that concomitant theophylline therapy significantly potentiated beclomethasone effects on lung function in the same patients [81]. These data suggest that additional doses of inhaled corticosteroid and/or alternative anti-inflammatory treatment may be required in asthmatic patients who smoke to overcome smoking-induced structural/inflammatory alterations and impaired corticosteroid sensitivity.

Studies investigating the effects of smoking on inflammation in asthma showed that that cigarette smoking affects airway inflammation by promoting neutrophilic inflammation and/or inhibiting eosinophilic inflammation [82–84]. However, some studies failed to document significant differences between smoker and non-smoker asthmatic patients [70, 82, 84]. Recently, a clinical trial enrolling 147 patients with asthma reported that asthmatic patients who smoke have increased bronchial epithelial remodelling (i.e. more goblet cells and mucus-positive epithelium, increased epithelial thickness and a higher proliferation rate of intact and basal epithelium) than ex-smokers and never-smokers. Interestingly, these enhanced airway remodelling correlated with the increase symptoms reported by smoker asthmatic patients. The same study also showed that smokers had higher numbers of mast cells and lower numbers of eosinophils than never-smokers in the airways in bronchial biopsies [85]. Therefore, cigarette smoke can enhance and modulate both airway remodelling and airway inflammation and these changes can be linked to poor response to treatment.

Several mechanisms have been described to explain how cigarette smoke can reduce sensitivity of inflammatory cells to corticosteroids in smokers with asthma. First, the non-eosinophilic sputum phenotype commonly found in smokers with asthma would be less responsive to corticosteroid therapy [86]. Second, there is a relative increase of the glucocorticoid receptor (GR) β (non-functional GR isoform) in peripheral blood mononuclear cells from current smokers compared with never-smokers asthmatic patients [87]. Third, reduced levels of histone deacetylases 2 (HDAC-2) were found in alveolar macrophages from smokers, which could lead to increased inflammatory gene expression and reduced sensitivity to corticosteroids in smokers with asthma [88, 89]. In addition, cigarette smoke induces bronchial epithelial damage/proliferation [90], mucous production [85] and impaired deposition of drug within the lungs [91]. Whether smoking can result in increased small airway impairment in asthmatic patients and whether the effects on small airway compartment contribute in reducing ability of inhaled corticosteroids to reach the pharmacological targets within the airways and thus response to therapy, is unknown.

There is evidence that cigarette smoke can induce airway inflammation and remodelling even in the absence of established airflow obstruction. Such a negative effect of cigarette smoke on the lung has been reported both in central [92–95] and in peripheral airways [96, 97] of subjects without any concomitant underlying chronic airway diseases. Moreover, a 13-year follow-up study showed that among smokers with normal lung function those showing functional abnormalities of the small airways compartment (as assessed by of nitrogen washout testing) experienced steeper lung function decline [98]. Taken together these data indicate that subjects who smoke develop airway abnormalities irrespective of the presence of airflow obstruction and it appears that these abnormalities antedate the development of airflow obstruction.

With this background, it would be important to assess whether asthmatic patients who smoke have greater impairment of the small airway compartment as the result of peripheral abnormalities related to both asthma and smoking. The clinical correspondence in terms of achievement and maintenance of asthma control should also be thoroughly investigated.

Conclusion and further directions

After several years of debate surrounding this topic, the contribution of small airway abnormalities in asthma pathobiology remains mainly unanswered. The role of small airways, as a relevant site for pathological abnormalities leading to increased airflow resistance in asthmatic patients, is supported by studies performed in the

past few decades [2–6]. However, whether small airway abnormalities have an impact in all asthmatics or only in some selected phenotypes is still an open question. Data pointing in the direction of a more prominent role of small airway impairment in some specific phenotype presentations are especially available when considering severe asthma. For these patients there is evidence of a correlation between the severity of the peripheral airway abnormalities and the severity of the clinical presentation [23, 35, 43]. Functional clues of small airway abnormalities have also been detected in elderly asthmatic patients, in particular, those with a long history of disease and/or fixed airflow obstruction, [67, 73]. Finally, cigarette smoke negatively affects small airways [96, 97] and thus smoking habit can result in amplified small airway abnormalities in asthmatic patients who smoke (Table 1).

The description of specific asthma phenotypes in which small airway abnormalities may play a relevant role raises the question of whether or not these patients would benefit from a pharmacological approach that, by ensuring a uniform distribution of the drugs in the airways, is able to also target the peripheral airway compartment. Notably, a number of studies published in previous years suggested that specific formulations of ICS or ICS/LABA (small particle or so-called 'extra-fine' formulations) can modify biomarkers/parameters related to small airways [99–102]. Specific randomized controlled studies are required to show that these treatments could represent a tailored therapy for selected phenotypes of asthmatics.

Therefore, to confirm the hypothesis that small airway inflammation can promote the development of specific asthma phenotypes, additional studies are required. First, studies able to phenotype patients for functional and pathological small airway abnormalities and to correlate these findings with clinical presentation are needed. Second, interventional studies with a tailored pharmacological approach in those asthma phenotypes with a prominent impairment would address the issue of whether targeting small airway abnormalities in patient's characterized by enhanced small airway disease results in any clinical benefit.

Acknowledgements

This publication has been supported by an unrestricted grant by Chiesi Foundation (Parma, Italy).

The authors thank Sara Panigone for her contribution and scientific assistance with the manuscript.

Conflict of interest: MC has received sponsorship from Chiesi Farmaceutici, Novartis, Menarini, Glaxo-SmithKline, Merck Sharp & Dome and AstraZeneca and he has been on Scientific Advisory Boards for Chiesi and Merck Sharp & Dome.

Table 1. Small airway abnormalities in specific asthma phenotypes

Asthma phenotype	Evidence of small airway involvement	Assessment technique/parameter
Severe asthma	Small airway inflammation	Autopsy specimens Transbronchial biopsies Alveolar NO measurement
	Premature airway closure and air trapping.	Lung function measurement (increased RV, RV/TLC, FRC; decreased FVC) Nitrogen washout measurement (increased CV, CC and slope phase III)
Asthma in the elderly	Premature airway closure, air trapping and decreased reversibility	Lung function measurements
Asthma in smokers	No direct evidence so far From knowledge of healthy smokers and COPD pathology: smoke causes alterations of small airways including inflammation and structural changes	

NO, nitric oxide; RV, residual volume; TLC, total lung capacity; FVC, forced vital capacity; FRC functional residual capacity; CV, closing volume; CC, closing capacity; COPD, chronic obstructive pulmonary disease.

MK has received sponsorship from Chiesi Farmaceutici Foundation; Research Funding (funds paid to Duke University) from GlaxoSmithKline, Merck, Genentech, Novartis, GE Healthcare and Astmatx.

QH has received sponsorship from Chiesi Farmaceutici, Genentech and GlaxoSmithKline.

JB has received sponsorship from Chiesi Farmaceutici, GlaxoSmithKline, Novartis, Astra Zeneca, UCB, Schering-Plough and Nycomed.

KFR has received sponsorship from Chiesi Farmaceutici, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Nycomed, Merck Sharp and Dohme, GlaxoSmithKline, Roche and AltanaPharma.

LMF has received sponsorship from Chiesi Farmaceutici, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed, Roche, Pfizer, Sigma-Tau, Menarini, Schering-Plough, Union Chimique Belge, Italian Ministry of Health and Italian Ministry for University and Research.

AP has received research funding from and/or has been on Scientific Advisory Boards for AstraZeneca, Chiesi Farmaceutici, GSK, UCB, Italian Ministry of Health and Italian Ministry for University and Research.

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