Drug Targeting in Bronchial Asthma: Inhaled Corticosteroids Should Reach the Peripheral Airways

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Abstract: Bronchial asthma is characterised by an eosinophilic inflammatory process in the airways, and manifests itself functionally by bronchial hyperresponsiveness and variable airflow obstruction. In the past this inflammatory process was presumed to be predominantly present in the large and intermediate airways. This is not surprising since functional abnormalities in the small airways (or so-called silent zone) are much more difficult to establish in comparison to changes in the larger airways. As a consequence, changes in airway calibre and bronchial hyperresponsiveness are mainly measured in the central part of the lung, i.e. by means of the FEV1 at rest or after challenge with bronchoconstrictive stimuli like histamine and methacholine. Recently, advanced physiological, radiological and morphological studies show that the inflammatory process extends to the peripheral airways and even the alveolar compartment. This so-called peripheral inflammation is related to the clinical manifestation of the severity of asthma. Targeting the small airways with new inhaled corticosteroids with a small particle size and a high peripheral deposition may result in better control of the disease. The presence and clinical consequences of peripheral inflammation and its therapeutic approach are discussed in this review.

INTRODUCTION

Bronchial asthma is characterised by an eosinophilic inflammatory process in the airways, and manifests itself functionally by bronchial hyperresponsiveness and variable airflow obstruction. In the long-term, airway remodelling may result in permanent damage and partly irreversible obstruction. In the past this inflammatory process was presumed to be predominantly present in the large and intermediate airways. This is not surprising since functional abnormalities in the small airways (or so-called silent zone) are much more difficult to establish in comparison to changes in the larger airways. As a consequence, changes in airway calibre and bronchial hyper responsiveness are mainly measured in the central part of the lung, i.e. by means of forced expiratory volume in one second (FEV1) at rest or after challenge with bronchoconstrictive stimuli like histamine and methacholine. More recent studies, however, show that the inflammatory process extends to the peripheral airways and even the alveolar compartment, and that this so-called peripheral inflammation is related to the clinical manifestation of the severity of asthma. These findings and their potential therapeutic consequences are discussed in this article. In particular, the effects of the formulation of inhaled corticosteroids (ICS) with small particle sizes are presented and analysed.

FUNCTIONAL CHANGES IN THE PERIPHERAL AIRWAYS

Functional alterations in the peripheral compartment of the lung have always been difficult to assess because changes in the calibre of the large airways always influence measurements of the patency of small airways. Only more sophisticated measures of small airway function allow assessment of the contribution of this compartment to the increased airway resistance in asthma. Bronchoscopy with measurement of flow and pressure in peripheral airways (by segmental occlusion) showed that the resistance in peripheral airways is markedly increased up to 80% of total airway resistance, even in patients with mild, asymptomatic asthma (Wagner ARRD 1990) [1]. By comparison, the contribution of the small airways to the total airway resistance in normal subjects is less than 10% (Hogg NEJM 1968) [2]. In addition, 'uncoupling' between lung parenchyma and airways occurs in the lungs of patients with asthma. This means that the normal presence of a reduction of airway resistance with increasing lung volume is absent in these patients (Irvin AJRCCM 2000) [3]. Besides, patients with asthma show a stronger tendency to collapse of the small airways (i.e. airway closure) during expiration (King AJRCCM 1998) [4]. Quantification of this phenomenon by a single-breath nitrogen washout test revealed that this occurs more frequently in patients with se-

vere asthma and recurrent exacerbations (in't Veen AJRCCM 2000) [5]. Finally, bronchial provocation with methacholine evokes marked small airways obstruction in a subgroup of asthmatics, which is associated with pronounced bronchial hyperresponsiveness in comparison to those patients who only react with large airways obstruction (Sekizawa ARRD 1986) [6]. Together, these findings demonstrate that there are important functional changes in the so-called silent zone of asthmatics that contribute to the clinical severity of asthma.

MORPHOLOGIC ALTERATIONS IN THEPERIPHERAL COMPARTMENT OF THE LUNG

Several morphologic studies have revealed that the aforementioned functional changes in the peripheral compartment of the lungs are caused by infiltration of this compartment of the lung with inflammatory cells. Specifically, both biopsies taken at autopsy, surgical specimens, peripheralbiopsies obtained by bronchoscopy and broncho-alveolar lavage (BAL) specimens have demonstrated that the typical 'asthmatic' inflammatory process with eosinophils and Tlymphocytesis present both in bronchioli (Hamid JACI 1997) [7] (Haley AJRCCM 1998) [8] and alveoli (van Vyve Chest 1992)[9](Kraft AJRCCM 1996) [10] (Kraft AJRCCM 1999) [11]. This peripheral inflammatory process is especially present in asthmatic patients with nocturnal airflow obstruction, i.e. 'nocturnal asthma'. In contrast, such changes are not observed in the central airway walls of these nocturnal asthmatics (Kraft AJRCCM 1996) [10] (Kraft AJRCCM 1999) [11]. Thus, asthmatics with nocturnal airflow obstruction differ from those without nocturnal obstruction by the presence of inflammatory cells in the peripheral compartment of the lung.

CLINICAL RELEVANCE OF PERIPHERAL INFLAMMATION

Significant correlations have been observed between the degree of nocturnal reduction of the FEV1 and the presence of inflammatory cells in the alveoli âĂŞ but not in the central airway wall in patients with nocturnal asthma (Kraft AJRCCM 1996) [10] (Kraft AJRCCM 1999) [11]. This part of the lung is the most important source of leukotrienes and (pro) inflammatory cytokines (Schulman JAP 1982) [12]; per mg tissue the lung parenchyma produces much more mediators involved in the cascade of the inflammatory process than the central airways. Besides, the small airways are very reactive upon stimulation with these mediators (Wolhsen AJRCCM 2001) [13]. The aforementioned correlations between peripheral inflammation and airflow limitation in nocturnal asthma probably also occur in more severe asthmatic patients, since nocturnal asthma is a phenotype of naturally fluctuating airflow limitation. Recently, Balzar and coworkers using transbronchial biopsies showed that intense inflammation occurs in the small airways of severe asthmatics (Balzar ERJ 2002) [14]. It should be noted, however, that – due to the severity of the disease – there are no studies at present directly exploring the relation between peripheral inflammation and clinical severity of the disease in severe asthmatics with recurrent exacerbations.

DO INHALED CORTICOSTEROIDS (ICS) REACH THE PERIPHERAL LUNG COMPARTMENT?

Administration of ICS is the cornerstone of the antiinflammatory treatment in asthmatic patients. After passing the oropharynx the majority of particles impact in the large and intermediate airways. This is related to the mass median aerodynamic diameter (MMAD) of the inhaled preparation. In particular particles with an MMAD less than 2 micrometer reach the peripheral compartment (Fig. (1)). Most dry powder inhalers(DPIs) and pressurised metered dose inhalers (pMDIs) deliver particles with an MMAD of 3–5 micrometer, or even higher if a inhalation of a DPI occurs at low flow rates (Pauwels ERJ 1997) [15].

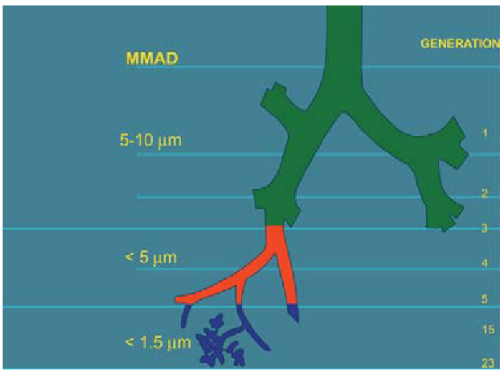

Fig. (1): Inhaled medication and lung deposition: relationship between airway generation and particle size (MMAD).

Recently an extra fine CFC-free solution of beclomethasone-dipropionate (extra fine HFA-

134aBDP, QvarTM has been developed. This pMDI fires particles with an MMAD of 0.9-1.1 micrometer (VandenBurgt JACI 2000) [16] (Leach Chest 2002) [17]. Besides, the inhalation device has been adapted, resulting in a $\sim$ 70% lower spray force in comparison to the traditional CFC-containing pMDIs (Gabrio IJP 1999) [18]. Together, these changes result in a high lung deposition of 50–60% of the label claim, in comparison to less than 15% with CFC-BDP and the CFC-containing pMDI with fluticasone propionate (FP) (Leach Chest 2002) [19] (Leach ERJ 1998) [17]. This is very well in line with the differences in MMAD between the preparations mentioned, i.e. extra fine HFA-134a-BDP, 0.9-1.1 micrometer; CFC-BDP, 3.5 micrometer; and CFC-FP, 2.0 micrometer (Leach Chest 2002) [17].

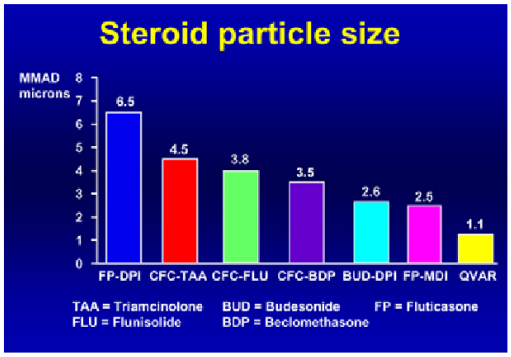

Fig. (2): MMAD of several inhaled corticosteroids.

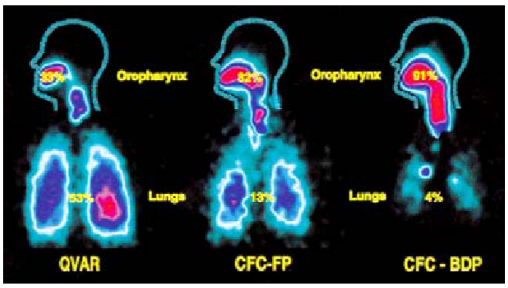

Fig. (3): Deposition of radio labeled after inhalation of extra fine HFA-134a-beclomethasone, cfc-fluticasone and cfc-beclomethasone.

Not only the amount of drug reaching the lower airways, but also the pattern of distribution of pulmonary deposition is important. Extra fine HFA134a-BDP has a relatively higher peripheral deposition compared with CFC-BDP and CFC-FP (Leach Chest 2002) [17]. This is of importance in terms of potential efficacy in the peripheral compartment of the lung, since the concentration of steroid receptors is highest in this part of the lung (Adcock AJRCCM 1996) [20]. Thus, an ICS with a low MMAD and thus high peripheral lung deposition may be expected to have more effects than an ICS with a higher MMAD and lower peripheral lung deposition.

ARE ICS ABLE TO MODULATE THE INFLAMMATORY PROCESS IN THE PERIPHERAL COMPARTMENT?

Mechanistic studies have been directed towards the question if ICS can modulate the inflammatory process in the peripheral compartment of the lung. CFC-FP was shown to reduce bronchial but not alveolar nitric oxide (NO) output in asthmatics, suggesting that the usual ICS do not influence inducible nitric oxide synthase (iNOS) expression in peripheral airways in these patients (Lehtimaki ERJ 2001) [21]. In another study, extra fine HFA-134aBDP, but not CFC-BDP, was demonstrated to modulate the immunologic reactivity of alveolar macrophages (Marshall ERJ 2000) [22]. A study using highresolution computed tomography (HR-CT) has shown that extra fine HFA-134a-BDP can attenuate regional hyperinflation induced by inhalation of methacholine in asthmatic patients, in contrast to CFC-BDP (Goldin JACI 1999) [23]. In addition, when HFA-134a-BDP and CFC-fluticasone were compared directly at a 1: 1 microgram ratio, HFA-134a-BDP showed superior effects on baseline closing volume (CV), CV/VC ratio, and postbronchodilator FEF 25–75% (Thongngarm J Asthma 2005; 42: 257-263) [24]. Together, these data indicate that the inflammatory process in the peripheral compartment of the lung can be modified by ICS with a low MMAD and high peripheral deposition in contrast to those with a high MMAD and low peripheral deposition, and that these changes are accompanied by functional improvements.

DO ICS WITH HIGH PERIPHERAL DEPOSITION IMPROVE CLINICAL OUTCOME?

One of the consequences of the application of ICS with a low MMAD and high lung deposition is that the dose delivered to the patient can be lowered compared with the dose of an ICS with a high MMAD and low lung deposition. Indeed, in a large clinical trial Busse et al. showed that the dose-response curve for a change in FEV1 and in measures of small airways patency (forced expiratory

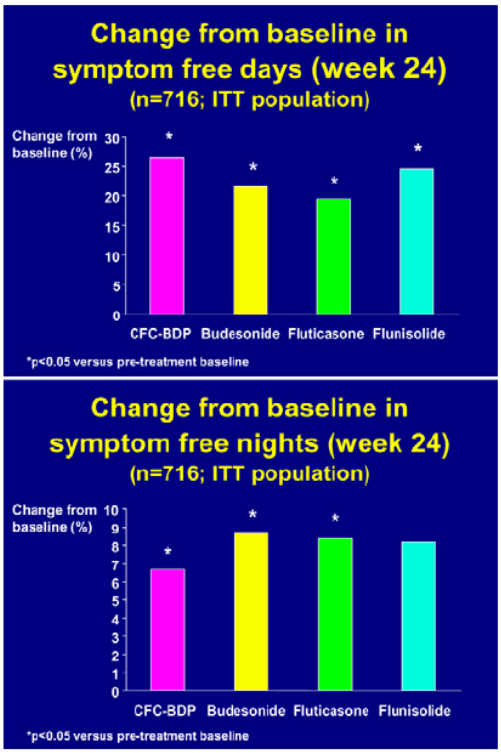

Fig. (4): Change from baseline in symptom free days (upper panel) and nights (lower panel) [39].

flow rate in the midexpiratory flow rate, FEF-25–75%) was shifted to the left with extra fine HFA-134a-BDP compared with CFC-BDP (Busse JACI 1999) [25]. It was calculated that it would take 2.6 times the dose of CFC-BDP to produce the same amount of improvement in FEV1 obtained with extra fine HFA-134a-BDP, and 3.2 times the dose of CFC-BDP to produce the same amount of improvement in FEF 25–75%. Several comparative studies have confirmed this 2: 1 dosage ratio in both adults (Davies RM 1998) [26] (Gross Chest 1999) [27] (Worth Respir 2001) [28] (Reichel IJCP 2001) [29] (Fireman AAAI 2001) [30] (Price Pharmacoeconomics 2002) [31] (Boulet CRJ 2004) [32] and children with asthma (Pedersen Ped 2002) [33] (Szefler JACI 2002) [34]. Besides, when extra fine HFA-134a-BDP was compared with CFC-FP, an ICS with an about 1.5-2 times higher potency than BDP, a 1: 1 ratio was demonstrated (Aubier RM 2001) [35] (Molimard Respir Med 2005) [36] (Lasserson Cochrane Database Syst Rev 2005) [37]. Of particular importance was the finding in several of these studies that extra fine HFA-134a-BDP resulted in significant improvements in quality of life, symptom scores and asthma control compared with the double dose of CFC-BDP or budesonide and a similar dose of CFC-FP, despite similar outcomes in lung function (Worth Respir 2001) [28] (Juniper Chest 2002) [38] (Ederle, Eur Rev Med Pharmacol Sci 2003) [39] (Van Schayck IJCP 2004) [40]. A significant improvement in asthma control has even been shown in patients receiving long-acting betaagonists besides their traditional ICS, suggesting potential advantages for HFA-134a-BDP extra fine aerosol as part of anti-inflammatory treatment optimization (Molimard Respir Med 2005; 99: 770778) [36]. Besides the benefits of increased peripheral deposition, another beneficial effect of extra fine HFA134a-BDP is its reduced oropharyngeal deposition (from 60-70% to less than 30%), resulting in less oropharyngeal side-effects (Thomp-son Respir Med 1998) [41]. It might be expected that increased lung deposition would be associated with increased systemic effects like suppression of cortisol production. Clinical comparative studies, however, have shown that this is not the case (Harrison JPP 1999) [42] (Boulet CRJ 2004) [32]. It has been postulated that this lack of cortisol suppression is associated with the pharmacokinetics of extra fine HFA-134a-BDP; due to its small particle size maximum serum concentrations after inhalation are higher but sooner reached compared with CFC-BDP(Tmax 30 min vs. 2–2.5 h, respectively). This low Tmax may affect the hypothalamic-pituitary-adrenal (HPA)-axis less, resulting in less adrenal suppression (Dekhuijzen RM 2000) [43] (Harrison J Aer Med 2002) [44].

CONCLUSIONS

There is increasing evidence that peripheral inflammation is present in patients with asthma, contributing to the clinical presentation of the severity of the disease. Mechanistic studies show that ICS with a low MMAD and a high peripheral lung deposition can modulate the immunologic and functional characteristics of the peripheral lung compartment, in contrast to ICS with a high MMAD and low peripheral lung deposition. This is reflected in a 2–2.5 lower dose of ICS required to achieve superior asthma control compared with the traditional ICS in both adults and children. The extend to which ICS with a low MMAD can achieve superior clinical efficacy besides the already demonstrated improvements in QOL in patients with severe asthma despite high doses of traditional ICS and oral corticosteroids is the subject of current studies.

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