

Effect of inhaled corticosteroids on small airway inflammation in patients with bronchial asthma

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KEY WORDS

asthma, inhaled corticosteroids, small airway inflammation

ABSTRACT

Bronchial asthma is a chronic inflammatory disease affecting the bronchial mucosa. In asthma patients, the highest number of inflammatory cells, including eosinophils, are found in the small bronchi. According to the most recent 2006 report of the Global Initiative for Asthma, inhaled corticosteroids (ICS) remain the first-line treatment of chronic asthma. They are characterized by high lung deposition and good distribution in the small bronchi, which makes them particularly efficient in reducing chronic inflammatory infiltrate in the small airways.

Good pulmonary distribution of ICS in patients with mild asthma is reflected by a better control of the disease, improvement in the quality of life, improvement in the results of pulmonary function tests, decreased levels of exhaled proinflammatory nitric oxide, lower number of inflammatory cells (including eosinophils) in the induced sputum, decrease in bronchial hyperreactivity, and decrease in exhaled air trapping observed in the computed tomographic scanning of the lungs.

Small bronchi – peripheral airways Small bronchi are often referred to in the scientific literature as peripheral or small airways. They constitute the largest part of the respiratory system and, therefore, the largest potential site of inflammation in patients with asthma and chronic obstructive pulmonary disease.¹ Small bronchi and bronchioles of 2 mm in diameter are located starting from the fourth down to the fourteenth subdivision of the bronchial tree; thus, the total respiratory surface of the peripheral airways is significantly increased.² In patients with asthma characterized by eosinophilic inflammation of the mucosa, the highest number of eosinophils are found in the small bronchi. Moreover, involvement of the small bronchi in chronic inflammation usually translates into increased bronchial hyperreactivity,³ more severe course of the disease, poor asthma control, and decrease in the quality of life.^{4,5}

In line with the most recent report of the Global Initiative for Asthma (GINA), which was published in 2006 and updated over the next several

years,⁶ disease severity no longer serves as a parameter for planning treatment strategy and has been replaced by the degree of control of the disease. The GINA report classifies patients into those with well controlled, partly controlled, and uncontrolled asthma. Inhaled corticosteroids (ICS) remain the first-line treatment in chronic asthma.⁶⁻⁹ A prescribed amount of a given ICS is based on the level of asthma control and, what follows, on the degree of inflammation, particularly in the peripheral airways. Initial treatment should include an intermediate dosage of ICS and, subsequently, should be modified according to the achieved level of control.¹⁰ Lack of response to ICS in severe asthma can signal changes in the expression of glucocorticoid receptor, impaired T-cell reactivity, and disturbed immunoregulation.¹¹

Asthma-related inflammatory infiltrate in the small bronchi The pathogenesis of asthma involves chronic inflammation^{6,8} mediated by migratory cells and structural cells releasing several

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proinflammatory mediators upon activation. Eosinophils, neutrophils, lymphocytes, macrophages, mast cells, epithelial cells, endothelial cells, smooth muscle cells, and fibroblasts all play their role in this process. Traditionally, eosinophils have been considered to be the main mediators of inflammation in asthma and to be responsible for epithelial damage, shedding of the bronchial mucosa, remodeling and fibrosis. Eosinophils are the source of a number of cytokines, including interleukin 5 (IL-5) and granulocyte-macrophage colony-stimulating factor, which promote differentiation of bone marrow stem cells into eosinophils. Several other cytokines produced and released by eosinophils contribute to bronchial inflammation in asthma: interleukins (IL-11, IL-13, IL-2, IL-4), eicosanoids (leukotriene C_4 , prostaglandin E_2 , thromboxane B_2 , 15-hydroxyeicosatetraenoic acid), interferon- γ (INF- γ), tumor necrosis factor (TNF), and transforming growth factor β , which is involved in promoting fibrosis. Nevertheless, recent studies involving the analysis of mucosal biopsies, bronchoalveolar lavage (BAL), and induced sputum have indicated that eosinophilic inflammation is not the only possible scenario here; in some cases, the cellular infiltrate is predominantly populated by neutrophils, a type of granulocytes responsible for fighting infection. They constitute the main source of IL-8, a chemokine with an ability to attract granulocytes, and leukotriene B_4 , eicosanoid attracting and activating neutrophils. Neutrophils express receptors for immunoglobulin E as well as HLA class I and II molecules; therefore, they can potentially present antigens as well as initiate and modulate an allergic immune response in patients with asthma exacerbated by simultaneous viral infection. Activated helper T cells are particularly important in orchestrating allergic inflammatory process in the bronchial mucosa. Depending on the pattern of produced cytokines, they can be divided into Th1 (IL-2, IFN- γ , TNF, IL-12) and Th2 (IL-4, IL-5, IL-3, IL-13) cells.

According to the classification published in 2007,¹² all cases of asthma can be divided into 4 phenotypic entities depending on the composition of the inflammatory infiltrate, determined on the basis of cellular composition of induced sputum. The values for healthy individuals are <1.9% for eosinophils and <61% for neutrophils.

Phenotypes of asthmatic inflammation are listed below:

- 1 eosinophilic: >1.9% eosinophils, <61% neutrophils
- 2 mixed >1.9% eosinophils, >61% neutrophils
- 3 neutropilic <1.9% eosinophils, >61% neutrophils
- 4 paucigranulocytic <1.9% eosinophils, <61% neutrophils.

Eosinophilic phenotype is the most common, and strictly correlates with atopy, bronchial hyperreactivity, and disease exacerbations. Although currently there is no unequivocal evidence supporting this hypothesis, it has been broadly

assumed that the response to the standard anti-inflammatory treatment with corticosteroids may depend on the diagnosed phenotype. It seems that eosinophilic inflammation is the one that is characterized by the best response to corticosteroid treatment.

The comparison of inflammatory infiltrate between the large and small bronchi is difficult due to their varying parameters and architecture.¹ A number of studies suggested that inflammatory infiltrate is much more pronounced in the small airways than in the large bronchi, while others claimed that there is no difference or even that the opposite is true, i.e., the infiltrate in the small airways is less evident. Such completely divergent results are probably the consequence of different methods used to assess the infiltrates as well as of the type of enumerated cells. Nevertheless, when compared with healthy individuals, asthma patients have significantly higher numbers of eosinophils, lymphocytes, and neutrophils, together with increased mRNA expression of IL-4, IL-5, and eotaxins in the peripheral airways.¹

Diagnostic methods in small airway inflammation

Lung function tests Lung function tests include:

- 1 increase in forced vital capacity (FVC) after β -mimetic inhalation
- 2 maximal expiratory flow (MEF) at various volume points of forced expiration (MEF₇₅, MEF₅₀, MEF₂₅), the most reliable parameter in assessing bronchoconstriction¹
- 3 the ratio of FVC to residual volume
- 4 dynamic lung compliance
- 5 closing volume (rarely used today).

Concentration of nitric oxide in expired air (fractional exhaled nitric oxide) as an indirect method of assessment

Chemiluminescence is used as the most common method of detecting nitric oxide (NO) in the exhaled air. NO is a known mediator of inflammation and its presence in the exhaled air is a marker of an ongoing inflammatory process of the bronchial mucosa in asthma, lack of disease control, or exacerbation of the disease. Moreover, regular use of ICS in patients with asthma results in decreased fractional exhaled NO (FE_{NO}). Measurement of NO as a marker of ongoing bronchial inflammation is a rather sensitive method, and the use of certain mathematical formulas can potentially allow us to distinguish between alveolar and bronchial air. FE_{NO} is a derivative of several contributors, including those that can be independent of the presence of eosinophilic inflammatory infiltrate in the airways.¹

Assessment of bronchial reactivity: bronchial challenge test with the use of nonspecific substances (adenosine monophosphate, methacholine, histamine)

Increased reactivity to nonspecific stimuli suggests an ongoing bronchial inflammation. The test is considered to be positive when the inhalation of a nonspecific triggering substance results in a decrease of the forced expiratory volume in 1

second (FEV₁) by 20% or more as compared with the baseline value. A provocation dose PD₂₀ or provocation concentration PC₂₀ is established as a dosage of methacholine or adenosine that leads to a 20% decrease in the FEV₁ value. Although a popular diagnostic tool, it is not specific and reflects inflammation process not only in the small but also in the large bronchi.¹

Cytological examination of late-phase induced sputum

In the first (induction) stage of this test, sputum is collected after nebulizing with the saline or hyperosmolar sodium chloride solution. In the second stage, sputum is processed and: 1) cytospin slides are prepared to assess the cellular components and 2) remaining supernatant is tested for soluble pro- and anti-inflammatory mediators. Methodology of the test and the following analysis of the sputum should strictly follow the European Respiratory Society guidelines published in the *European Respiratory Journal* in 2002,¹³ and those of the Polish Society of Lung Diseases published in 2008.¹⁴ A thorough cytological analysis of late-phase induced sputum enables differentiation between various asthma phenotypes according to the predominant cell type within the infiltrate, e.g., eosinophils, neutrophils, or other cells. Sputum obtained in this method is usually derived from the central bronchi.¹

Oscillometric measurement of pulmonary resistance

Oscillometry assesses the changes in gas flow through the airways induced by a known varying external pressure. It measures the parameter of impedance, which consists of two elements reflecting the relationship between pressure and flow: resistance and reactance. While resistance is mainly dependent on unobstructed airways, reactance reflects pulmonary elasticity.¹⁵ Impulse oscillometry system (IOS) and forced oscillation technique are the two most common methods for assessing bronchospasm and bronchial hyperreactivity.^{15,16}

High-resolution computed tomography of the chest

High-resolution computed tomography is currently the most precise imaging technique able to visualize the pulmonary tissue. Selecting appropriate parameters and adjusting the window of interpretation allows to determine the thickness of the bronchial wall, potential remodeling process, as well as expiratory lung volume (expiratory lung volume computed tomography). Diminished expiratory lung volume can be a sign of "air trapping", namely, an increased volume of residual air and subsequent distention of the lung due to bronchoconstriction.¹⁷ Importantly, bronchial wall remodeling always has to be considered while assessing potential bronchial obturation.

Bronchoscopy Various cytokines as well as pro- and anti-inflammatory mediators can be easily detected in the epithelial lining fluid and the BAL fluid.¹⁷ Similarly to the induced sputum, BAL

usually contains central bronchi-derived material.¹ Transbronchial biopsy of the mucosal membrane is a more sensitive, but definitely more invasive, method of assessing the inflammatory infiltrate *in situ*.

Level of deposition of inhaled corticosteroids in the small bronchi

Distribution of ICS in the lung, and especially their deposition in the small bronchi, is particularly important for good asthma control and for the improvement of the quality of life.¹⁸ In humans, the diameter of small bronchi is below 2 mm, while their inner surface increases in a linear manner with each subsequent division. Due to the anatomical conditions (and without even mentioning the fact that the activity of allergic inflammation is the highest in the peripheral bronchi) corticosteroid inhalers should be directed predominantly to the periphery. Pulmonary deposition and distribution of the ICS-containing aerosol depends on the presence of small, dispersed molecules in the total volume of released medication.

It has been proved that the most efficient delivery of the inhaled medication to the small airways can be achieved using metered-dose/hydrofluoroalkane inhalers. They produce aerosol of which 50% are droplets smaller than 1.1 µm. Such droplets have the highest capacity to travel through the anatomical throat barrier (high value of total pulmonary deposition) and are characterized by high potential to be deposited in the bronchi smaller than 2 mm (high deposition in the small bronchi) and deliver a potent ICS exactly where it can exert its anti-inflammatory action.

Ciclesonide is an inhaled glucocorticoid (1.1–2.1 µm), characterized by high availability for the small bronchi and, therefore, by high anti-inflammatory efficiency. In an inhaler, it is present as a biologically inactive pro-drug without the ability to bind the glucocorticoid receptor, and is diluted in a freon-free carrier, hydrofluoroalkane. As much as 65% of the drug leaving the inhaler during its administration reaches the lungs, 10% is removed from the peripheral airways while exhaling, and the remaining 55% is deposited in the respiratory system. Ciclesonide is highly lipophilic and therefore deposited in the lungs in a prompt and uniform manner. In the airways, pro-drug becomes enzymatically cleaved to des-ciclesonide (des-CIC), a derivative characterized by potent anti-inflammatory properties. Subsequently, des-CIC reaches the bloodstream where it is almost entirely bound to plasma proteins. Approximately 1% of the active drug reaches the peripheral tissues and organs as a free fraction. The level of deposition and the amount of active drug reaching the small bronchi determine its efficiency in limiting the ongoing inflammation as well as achieving a prolonged period of remission/amelioration.^{19–21}

Direct evidence points to the exceptionally good deposition and distribution of ciclesonide, particularly in the peripheral airways.²² In a study on

healthy volunteers, lung deposition of ^{99m}Tc -labelled ciclesonide was significantly higher than its deposition in the mouth and throat (52% vs. 32%, respectively). Moreover, the average percentage of drug deposited in the peripheral airways including alveoli was higher than in the large bronchi (47% vs. 17%, respectively). Two-dimensional (2D) gamma scintigraphy and three-dimensional single-photon emission computed tomography were used to measure deposition of ciclesonide in the lungs, bronchi, mouth, and throat. Pharmacokinetics of ciclesonide and its active metabolite (des-CIC) was analyzed using liquid chromatography-tandem mass spectrometry. Concentration of both substances was measured in mouth-rinsing solutions. The pharmacokinetic profile of both Tc-labeled and unlabeled ciclesonide was similar.²³ The drug was administered through hydrofluoroalkane-metered dose inhaler.

A similar study was conducted in 12 patients diagnosed with mild asthma with the mean FEV₁ values of approximately 95%. After a single inhaled 320 µg dose of ^{99m}Tc -labeled ciclesonide, the deposition and distribution of the drug was measured by 2D gamma scintigraphy. Ciclesonide deposition was significantly higher in the lungs than in the mouth and throat (52% vs. 32.9%, respectively).²⁴ Additionally, ciclesonide has been reported to be well tolerated in children and to improve spirometric values and the quality of life of the patients while administered by a metered-dose inhaler with or without a spacer.²⁵

Efficiency of inhaled corticosteroids in small airway inflammation in asthma

Anti-inflammatory effect of ciclesonide (80 or 160 µg/daily in a single dose) was compared with the effect of 100 µg/daily in a single dose of fluticasone in patients with mild asthma.²⁶ Regardless of the dosage, after 2 weeks of therapy with ciclesonide, there was a significant decrease in the level of NO in the expired air as compared with fluticasone. Such strong effect was not observed in the group treated by fluticasone even after 8 weeks of inhalation therapy, suggesting more potent anti-inflammatory action of ciclesonide. Nevertheless, the FEV₁ values and clinical symptoms improved and the use of fast-acting β_2 -mimetics on demand was reduced in all study groups, regardless of the administered glucocorticoid.

A further analysis of ciclesonide's ability to limit the inflammatory process in the small bronchi was described in a study published recently by Hoshino.²⁷ Patients with mild asthma were administered either fluticasone (100 µg twice a day) or ciclesonide (200 µg once daily) for 8 consecutive weeks. IOS and the measurement of eosinophil percentage in induced sputum were used to assess inflammatory process in the small airways. A decrease or elimination of the inflammatory process in the small airways was significantly more pronounced in the group treated with ciclesonide compared with fluticasone, as indicated by a significant decrease in small airway resistance

(R5–R20, $P < 0.05$), distal reactance (X5, $P < 0.01$), reactance area (AX, $P < 0.01$) and decreased levels of sputum eosinophils ($P < 0.01$).

Several publications underline the beneficial anti-inflammatory effects of ICS, especially ciclesonide,^{28,29} but also of fluticasone.²⁸ Importantly, they inhibit or decrease the development of early and late phases of the allergen-induced bronchospasm, limit the extent of the inflammatory infiltration of the bronchi by decreasing the number of inflammatory cells, especially eosinophils and lymphocytes, and act to prevent future remodeling of the bronchial wall.

Conclusions Deposition of the drug in the small bronchi and its resulting local availability influence the efficiency of its anti-inflammatory effects and its pharmacodynamics. Ciclesonide seems to fulfill all the criteria of being the drug of choice for patients with mild asthma; currently, it has one of the best deposition patterns compared with placebo^{17,30} or other ICS.^{26,27} Furthermore, it improves the chances of achieving better disease control, improves the quality of life, increases the values of pulmonary function tests, decreases the levels of proinflammatory NO in the exhaled air, decreases the number of cells in the inflammatory infiltrate, including eosinophils, decreases the bronchial hyperreactivity by increasing the PD₂₀, and decreases the expiratory air trapping observed in the computed tomographic scanning of the lungs.

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Wpływ kortykosteroidów wziewnych na zapalenie w drobnych oskrzelach u chorych na astmę oskrzelową

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SŁOWA KLUCZOWE

astma,
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drobnych oskrzeli

STRESZCZENIE

Astma oskrzelowa jest przewlekłą chorobą zapalną błony śluzowej oskrzeli. U chorych na astmę największa liczba komórek zapalnych, w tym eozynofików, znajduje się w drobnych oskrzelach. Zgodnie z najnowszym raportem Światowej Inicjatywy Zwalczania Astmy (Global Initiative for Asthma – GINA, 2006) w astmie przewlekłej lekami pierwszego rzutu pozostają kortykosteroidy wziewne (*inhaled corticosteroids* – ICS). ICS charakteryzują się dużą depozycją płucną i dobrą dystrybucją do drobnych oskrzeli, dzięki czemu skutecznie zmniejszają przewlekły naciek zapalny, szczególnie w drobnych oskrzelach.

O dobrej dystrybucji płucnej ICS u chorych na umiarkowaną astmę świadczą: kontrola choroby, poprawa jakości życia pacjenta, poprawa wartości badań czynnościowych płuc, zmniejszona ilość tlenu azotu – substancji prozapalnej – w wydychanym powietrzu, zmniejszona ilość komórek zapalnych (w tym eozynofików) w płwocinie indukowanej, zmniejszona nadreaktywność oskrzeli oraz zmniejszona pułapka powietrza na wydechu widoczna w badaniu tomografii komputerowej płuc.

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