Anti-inflammatory drugs in asthma therapy

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Abstract

Asthma is a chronic inflammatory disease. Pharmacologic management of asthma comprises long-term treatment to suppress the airway inflammation and quick-relief treatment to provide prompt reversal of acute bronchoconstriction and its accompanying symptoms. Anti-inflammatory agents are of crucial importance in asthma therapy. The most potent and effective medications used for long-term treatment of asthma are inhaled corticosteroids. Other medications, like: cromones, leukotriene antagonists and theophylline also show, but much less, anti-inflammatory activity. They can be used alternatively to inhaled corticosteroids in patients with mild persistent asthma but they are less effective. The add-on therapy with those medications should be considered if asthma control is not achieved with initial inhaled corticosteroid therapy. The combination treatment with long-acting β_2-agonists and inhaled corticosteroids has become the treatment of choice for the majority of asthmatic patients and nowadays constitutes the new "gold standard" of asthma therapy.

Key words: *anti-inflammatory agents, inhaled corticosteroids, leukotriene antagonists, long-acting β_2-agonists, theophylline, cromones*

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Bronchial asthma is a chronic inflammatory disease characterized by reversible airways obstruction, airways inflammation and increased airways responsiveness to a variety of stimuli. Clinical and experimental studies have shown the contribution of the airways inflammation to clinical course and severity of asthma. Anti-inflammatory drugs are therefore of major importance in the treatment of all varieties of asthma. Their long-term use is the only way to reduce bronchial hyperresponsiveness and asthma symptoms.

Inhaled corticosteroids are the most effective anti-inflammatory agents used for treatment of asthma. They are therefore drugs of choice in therapy of persistent asthma including its mild variety. Other drugs used in asthma management like nedocromil sodium, cromolyn sodium, leukotriene modifiers and theophylline also show, although much less, anti-inflammatory action. *In vitro* studies have demonstrated anti-inflammatory activity of β_2-agonists, however this has not been proved by clinical trials so far.

According to the GINA 2002 (Global Initiative for Asthma) expert panel report the disease treatment should be individual and matching asthma severity. To classify the asthma severity combined assessments of lung function, symptoms as well as the level of medication regimen, if the patient is already on treatment, are required [1].

The primary goal of asthma therapy is to maintain full control of the disease, which is possible to achieve in most patients. In well-managed asthma the symptoms are minimal or none at all, also at night and the patient is not limited in daily activities. Pulmonary function is normal or close to normal. There are no exacerbations of asthma and no need for emergency department visits or hospitalizations. The use of short-acting beta2-agonists for relief of acute symptoms is minimal. The last but not least goal is to provide the therapy for asthma with minimal or no side effects.

Anti-asthma medications are now categorized into two general groups: long-term control medications and relief medications. The first are used daily to maintain long-term asthma control as opposed to relievers which should be used only in case of asthma symptoms exacerbation. The most effective anti-inflammatory medications for suppression of allergic inflammation and for maintenance of asthma symptoms are inhaled corticosteroids.

Inhaled corticosteroids

The role of corticosteroids (CS) in bronchial asthma treatment is well established. It is nowadays assumed that

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anti-inflammatory effect of corticosteroids is mainly due to their ability to inhibit the expression of multiple inflammatory genes for cytokines, adhesion molecules, enzymes and receptors. The inhibition of allergic inflammation has been shown as a result of:

- direct inhibition of genes transcription for inflammatory mediators [2, 3],
- direct induction of genes transcription for β-2 receptor, lipocortine and neutral endopeptidase [4–7],
- inhibition of inflammatory genes for cytokines, adhesion molecules and enzymes by inactivation of transcription factors (AP-1, NF-κB) as a result of direct interaction of these factors with receptor-CS complex [8] or induction of synthesis of inhibitors for these factors (I-κB) [9],
- reduction the stability and enhancement of degradation of mRNA for inflammatory cytokines (IL-1β, IL-6, IL-8, INF-γ) [10, 11].

Glucocorticoid receptor (GR) – glucocorticoid (GS) complex, making a transcription factor, binds to a nucleotide sequence of the regulatory region of DNA called glucocorticoid response element (GRE). Binding of GR-GS and GRE may result, as mentioned above, in two opposite effects – enhancement or inhibition of gene expression and protein synthesis. The influence on gene transcription is achieved by allowing or preventing RNA polymerase access to gene promoter. It has been assessed that the number of genes within a cell which can be activated or inactivated by corticosteroids reaches up to 100 [12]. Besides the inhibition of pro-inflammatory mediators activity, the ability of corticosteroids to increase the β_2-receptor gene transcription and the synthesis of β_2-adrenergic receptors seems to be of great importance. This mechanism compensates for the loss in receptor membrane density resulting from "down-regulation" of pulmonary β_2-adrenergic receptors caused by chronic exposure to β_2-agonist. Many different inflammatory cell types have been implicated in the pathogenesis of asthma. As confirmed by a variety of *in vitro* studies corticosteroids may have direct inhibitory effect on the most important cells involved in airway inflammation. Enhanced apoptosis and reduced recruitment of cells to the site of inflammation decrease the number of eosinophils in circulation and airways in patients suffering from asthma [6, 13]. Corticosteroids also inhibit the release of mediators and cytotoxic proteins from eosinophils [14]. Corticosteroids do not inhibit degranulation of mast cells [15], but due to inhibition of IL-3 gene expression and enhancement of cell apoptosis can reduce the number of mast cells within the airway [16]. They also reduce the number and release of inflammatory mediators from lymphocytes [13] and macrophages [17]. Corticosteroids have also an inhibitory effect on epithelial cells, which are the source of inflammatory cytokines and contribute to the allergic inflammation. Treatment with corticosteroids inhibits the transcription of RANTES, IL-8 [18–20] as well as endothelin, phospholipase A2, cyclooxygenase and nitric oxide synthase. Corticosteroids lessen mucus secretion in inflamed airways by direct action on mucosal glands [20]. They also reduce plasma leakage from airway capillaries [21] by inhibition of expression of NO synthase gene. Finally corticosteroids have inhibitory effect on airway allergic inflammation in asthma by decrease in number of cells involved in the process, mostly eosinophils, mast cells, lymphocytes and macrophages, inhibition of their activity, and additionally by decrease in mucus production and micro-leakage from postcapillary venules. Several clinical studies have fully confirmed effectiveness of inhaled corticosteroids in inhibition of allergic inflammation as well as in asthma treatment. They are used in long-term therapy of all varieties of chronic asthma, including the mild persistent asthma [22]. That is because the inflammation is a feature of even early stage of the disease. Treatment with corticosteroids allows to reduce bronchial hyperresponsiveness [23], to decrease in symptom scores and in usage of short-acting β_2-agonists and also to improve lung function [24]. In severe asthma they allow to reduce the need for oral corticosteroids or even to withdraw the oral drugs completely with concurrent maintenance of asthma control [25]. Treatment with corticosteroids also reduces the need for hospitalizations and mortality from asthma both in children and adults. It is noteworthy that corticosteroids are the only drugs that can inhibit remodeling of bronchi, though they cannot reverse this process [26]. Corticosteroids are nowadays the drugs of choice in bronchial asthma therapy. They allow not only effective control of the allergic inflammation but also improvement in asthma symptoms and in health related quality of life.

Cromones

Cromolyn sodium and nedocromil sodium are other representatives of anti-inflammatory drugs used in asthma treatment. *In vitro* studies have demonstrated that the mechanism of cromones action is based on the inhibition of chloride ions influx through chloride channels. By inhibition of chloride ions influx cromones prevent cells from activation and reverse the degranulation. The drugs have been shown to exert their effect on many inflammatory cells, airway epithelial cells and sensory nerves [27]. Studies on anti-inflammatory effect of cromolyn sodium are scarce [28–31]. The decrease in number of eosinophils, mast cells, T-lymphocytes and macrophages in bronchial biopsy in patients with mild and moderate atopic asthma after 12 weeks of treatment with cromolyn sodium was reported. Cromolyn sodium was also shown to decrease significantly the expression of adhesion molecules ICAM-1, VCAM-1 and ELAM-1 [32]. Clinical studies demonstrated the positive effect of treatment with cromolyn sodium on lung function, improvement of asthma symptoms and also inhibition of both early and late allergen-induced asthmatic responses. It was also shown, that long-term treatment with cromolyn sodium (over 12 weeks) inhibits bronchial non-specific hyperresponsiveness in patients with asthma [33]. Shorter treatment (up to 6 weeks) protects atopic

asthma patients against enhancement of allergen-induced bronchial hyperresponsiveness during the pollination period of grass [34].

Nedocromil sodium is of much broader action. It inhibits the activity of many inflammatory cells, i.e. mast cells, eosinophils, monocytes, macrophages and platelets [35]. Nedocromil sodium inhibits the release of inflammatory mediators: eosinophil cationic protein (ECP), major basic protein (MBP) and LTC4 [36] from eosinophils. Nedocromil sodium also blocks the IgE dependent release of histamine from lung mast cells obtained from bronchoalveolar lavage fluid (BALF) [37]. The inhibition of the pro-inflammatory cytokines IL-8, GM-CSF, TNFα release and the decrease in expression of antigen HLA-DR on airway epithelial cells was also demonstrated [38, 39]. Nedocromil sodium was shown to reduce significantly IgE synthesis. Clinical efficacy of nedocromil sodium was well documented. In patients treated with this drug lung function improvement, reduction of asthma symptoms and inhibition of bronchial hyperresponsiveness and both early and late asthmatic reactions to allergen challenge were demonstrated [40–42]. Lately, the 4-week study in children with moderate asthma treated with nedocromil sodium has also confirmed the clinical effectiveness of the drug. This study additionally demonstrated the significant decrease in total serum concentration of IgE, IL-4, sIL-2R and sICAM [43]. Combination therapy with nedocromil sodium and inhaled corticosteroids in patients with persistent asthma allows reduction of corticosteroids dosage [44, 45]. It must be stressed however, that cromones do not affect remodeling of airways. Because they are safe, with no major side effects, they are still of wide use, mainly for mild asthma treatment in children.

Antileukotriene agents

Antileukotriene agents have been introduced for asthma therapy over the past few years. There are actually two drugs: zafirlukast and montelukast available on Polish market. Zafirlukast and montelukast are leukotriene receptor antagonists. They bind specifically to Cys-LT1 receptor and in this way block the action of cysteinyl leukotrienes (LTC4, LTD4 and LTE4). Many studies have shown that inflammatory process in airways is accompanied by a significant increase in synthesis and release of leukotriene. The increase in leukotriene concentration in bronchoalveolar lavage (BAL) fluid, serum and urine was demonstrated [46, 47]. Cysteinyl leukotriene receptor antagonists have been shown to have a bronchodilator action (FEV1 increase of 10–15%) and to attenuate the exercise, LTD4 and cold air induced bronchoconstriction. In patients with aspirin-induced asthma they protect against aspirin-induced bronchoconstriction [48]. Leukotriene receptor antagonists also possess anti-inflammatory activity, although they are much less effective than corticosteroids. A simple dose of 40 mg of zafirlukast administered orally 2 hours prior to allergen challenge blocked early and late asthmatic response by 80% and 50%, respectively. It also inhibits bronchial hyperresponsiveness to inhaled allergen challenge [49]. Calhoun et al. demonstrated significant decrease in histamine concentration, number of mast cells, basophils and lymphocytes in BAL fluid 48 hours after allergen challenge in asthmatic patients treated with zafirlukast (40 mg/day for 7 days) [50]. Clinical studies confirmed that long-term use of zafirlukast results in improvement in daytime asthma symptoms, frequency of night awakenings and use of β_2-agonists [51]. It also improves lung function (morning PEF, FEV1) and decreases bronchial hyperresponsiveness and number of asthma exacerbations. Add-on studies with corticosteroids have shown the efficacy of combination therapy and possible optimal control of asthma in most patients. [52]. It is to be stressed that zafirlukast is well tolerated and have a low incidence of side effects.

Another anti-leukotriene agent available on the market is montelukast. Like zafirlukast, it inhibits early and late asthmatic response, protects against exercise-induced bronchoconstriction, and decreases the number of asthma exacerbations. Kuna et al. have showed significant improvement of asthma control in patients with aspirin-intolerant asthma after 4 weeks treatment with montelukast [53]. Montelukast also demonstrates anti-inflammatory action, as shown by decrease in number of circulating and sputum eosinophils. Studies in asthmatic children treated with montelukast have demonstrated besides improvement in lung function and in asthma control accompanying decrease in eosinophils, ECP, IL-4 and sICAM blood concentration [54]. Montelukast was also found to have an inhibitory effect on GM-CSF synthesis in peripheral blood mononuclear cells in patients sensitized to grass pollen [55]. In asthmatic children treated with montelukast the significant decrease in exhaled nitric oxide concentration was observed [56].

In studies carried out on rats montelukast has been shown to decrease the number of eosinophils and lymphocytes in BAL fluid as well as to decrease endotheline-1 and IFN-γ serum concentrations by 30% and 72%, respectively [57]. Using mouse asthma model, inhibitory effect on airway inflammation and bronchial remodeling after allergen challenge was observed [58]. Clinical studies in asthmatic patients have confirmed positive effect on asthma control of montelukast added on to inhaled corticosteroid therapy (beclomethasone 400 mcg/day). Patients treated with montelukast compared with the placebo group experienced significant improvement in daytime symptom scores and FEV1 as well as significant decrease in number of night awakenings. [59].

Lofdal et al. study has showed that treatment with montelukast added on to inhaled corticosteroid therapy allows reduction of corticosteroids dosage by 47% with no negative influence on asthma control [60]. Similar studies

in children, have also demonstrated that added on therapy with montelukast to inhaled budesonide resulted in asthma symptoms and spirometry parameters improvement and in decrease in asthma exacerbations. [61].

One of the most recent studies, however, failed to confirm additional benefits of adding montelukast (10 mg/day for 2 weeks) to inhaled corticosteroids in patients with moderate and severe asthma. No significant improvement in parameters of efficacy including morning peak expiratory flow in montelukast group was demonstrated [62]. It is also noteworthy, that attempts to switch therapy from low dose inhaled corticosteroids to anti-leukotriene agents may result in much less effective asthma control and increase in number of hospitalizations [63]. Last years studies have reported on the possibility of Churg and Strauss syndrome development during the treatment with leukotriene receptor type I antagonists. These cases comprised only patients in whom oral corticosteroids therapy had been withdrawn. Recently, the syndrome has been however described in patients never treated with corticosteroids [64, 65]. So far there is no clear evidence for connection between Churg and Strauss syndrome and anti-leukotriene therapy. The issue will require further investigation.

The anti-leukotriene agents are well tolerated with low incidence of side effects and appear to be useful controller medications. They are administered orally in the form of tablets. They can be used in all varieties of persistent asthma: mild, moderate and severe.

Theophylline

In spite of many years of using theophylline in clinical practice and many studies on this field the pharmacological mechanism of theophylline action has not been fully elucidated. Theophylline is a non-selective inhibitor of phosphodiesterase (PDE), enzyme responsible for decomposition of cyclic nucleotides in cells. This action results in intracellular increase in cAMP and cGMP concentration. Over the past few years anti-inflammatory and immunomodulatory activity of theophylline was reported. As has been shown *in vitro* theophylline inhibits histamine release from mast cells and basophils. It also affects other inflammatory cells like: monocytes/macrophages, eosinophils and neutrophils. *In vitro* theophylline blocks release of mediators TNFα and LTB_4 from human monocytes and hyperoxide anions from BAL fluid macrophages.

Theophylline protects against eosinophils degranulation and inhibits eosinophil cationic protein (ECP) and eosinophil derived neurotoxin (EDN) release. Theophylline affects also production of active oxide compounds and metabolites of arachidonic acid by eosinophils. Theophylline blocks the activity of neutrophils and LTB_4 release. *In vitro* studies have also shown that the drug inhibits IL-2 production by T-lymphocytes and IL-2 dependent lymphocyte proliferation [66, 67].

In clinical studies in atopic asthma patients treated with theophylline within 6 weeks (200 mg b.i.d.) lesser late asthmatic response after challenge with inhaled allergen was found [68].

However, the study results on theophylline action on bronchial hyperresponsiveness are ambiguous. Some authors reported no protective effect of theophylline on bronchial hyperresponsiveness after challenge with specific allergen, while others reported significant differences in comparison with placebo [69–71]. Treatment with theophylline resulted in significant decrease in number of activated eosinophils in bronchial mucosa biopsies obtained 24 hours after allergen challenge [68]. Significant influence of theophylline on number of activated T-lymphocytes (CD_4^+ HLA-DR^+, CD_4^+ $CD25^+$) and activated eosinophils *in sputum* samples were also observed [72]. Kidney at al. reported the worsening of asthma symptoms after theophylline withdrawal in patients treated with high-dose inhaled corticosteroids and theophylline. This was accompanied by decrease in number of activated T-lymphocytes (CD_4^+ and CD_8^+) in circulation and parallel increase of those T-lymphocytes in bronchial mucosa biopsies. The observation suggests that theophylline inhibits the recruitment of T-lymphocytes to airway mucosa [73]. Another study has shown the significant decrease in number of T-lymphocytes CD_8 and cells containing IL-4 and IL-5 in bronchial biopsy samples derived from patients suffering from moderate asthma and treated with theophylline [74]. Importantly, anti-inflammatory action of theophylline was noticed with concentrations of 5–10 μg/mL. This allows use of lower doses and reduction of possible side effects of treatment observed with higher concentrations (10–20 μg/mL). Clinical study on efficacy of theophylline (Theodur 200 mg b.i.d.) and inhaled budesonide (Pulmicort 200 μg b.i.d.) in asthma treatment has shown that budesonide is more effective than theophylline in control of night symptoms [75]. Also treatment with fluticasone propionate (100 or 200 μg/day) resulted in better improvement of lung function (FEV_1, PEF) compared to theophylline [76]. Other studies reported similar clinical effect of theophylline (11 μg/mL in serum) and budesonide (800 μg/day) [77] as well as theophylline and beclomethasone dipropionate (320 μg/day) [78]. Better control of steroid-dependent asthma and steroid sparing effect was obtained with add-on treatment with theophylline [79, 80]. One of the most recent studies has demonstrated that long-term treatment with inhaled budesonide (800 μg or 200 μg b.i.d.) was much more effective compared to theophylline treatment (Theo-Dur 300 mg b.i.d.) in patients with mild and moderate asthma. In patients treated with inhaled steroids significant lung function improvement (FEV1), the decrease in airway hyperresponsiveness to histamine and asthma symptom scores reduction was observed. In the theophylline group neither lung function improvement nor reduction in bronchial responsiveness to histamine could be noticed. These results indicate the advantage of inhaled steroids over theophylline in asthma control [81]. It is noteworthy that theophylline does not affect airway remodeling in asthmatic patients.

According to GINA 2002 report add-on to inhaled corticosteroids therapy with theophylline is less effective (Evidence A) but at the same time less expensive than add-on therapy with long-acting β_2-agonists.

Combination therapy with long-acting β_2-agonists (LABA) and inhaled corticosteroids

There are two currently available long-acting β_2-agonists: salmeterol and formoterol. They belong not only to relief medication group but also to long-term asthma controllers. Mechanism of action is based on β_2-adrenergic receptor activation, adenyl cyclase activation, intracellular increase of cAMP concentration and finally protein phosphorylating kinases activation. Activation of β_2-adrenergic receptors results in airway smooth muscle relaxation, enhanced mucus production, reduced acetylocholine release from cholinergic nerves terminations, reduced neuropeptides release from sensory nerves terminations and decrease in leakage from capillaries. *In vitro* studies have shown anti-inflammatory activity of β_2-agonists [82, 83]. However, clinical studies have not confirmed clearly these observations. Roberts et al. have not noticed any effect of 6-weeks treatment with salmeterol on number and activity of BAL fluid eosinophils and lymphocytes as well as on inflammatory mediators concentrations (PGD2, histamine and tryptase) [84]. Similarly, 8-week treatment with formoterol had no effect on number of activated lymphocytes in bronchial mucosa biopsy [85]. Other clinical studies also have not confirmed anti-inflammatory action of long-acting β_2-agonists in bronchial asthma monotherapy. However, it has been shown that adding a LABA to inhaled corticosteroids results in additive anti-inflammatory effect. According to Greening et al. the combination of salmeterol and beclomethasone in patients with symptomatic asthma was more efficient than doubling the dose of inhaled corticosteroid [86]. Similarly Woolcock et al. reported that combination therapy (salmeterol with beclomethasone) was more effective than therapy with beclomethasone alone, even in high dose [87]. It was also shown that formoterol added to inhaled budesonide reduced the number of mild and severe asthma exacerbations [88]. These results have recently been mirrored in a similar trial design with salmeterol and fluticasone. This combination therapy improves lung function, reduces the number of asthma exacerbations and improves health related quality of life [89–91]. The combined approach to therapy not only provides better overall control of asthma but also allows decrease in corticosteroids dosing [92].

The combination treatment with long-acting β_2-agonists and inhaled corticosteroids has become the treatment of choice for the majority of asthmatic patients and nowadays constitutes the new ”gold standard” of asthma therapy.

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