CLINICAL STUDY

# Current opinions on the role of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease

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**Abstract**

***Background:*** **Chronic obstructive pulmonary disease (COPD) is one of the main cases of mortality and morbidity of population worlwide. In spite of enormous efforts there are not pharmacological agents evidently influencing natural course of disease available. Besides looking for new drugs influencing the long term outcome of patients with COPD, there is also running the process of reevaluation of the role of several already established drug groups.**
***Methods:*** **Through the use of recent knowledge and results from large-scale clinical studies as well as metaanalyses we give a view on action of inhaled corticosteroids in the pathophysiological mechanisms of COPD and complex summary of their role in the therapeutic management of the disease.**
***Conclusion:*** **Contrary to systemic corticosteroids, agreement regarding usage of inhaled corticosteroids necessary by acute exacerbations of disease has not been reached yet. Recent meta-analyses of the long-term clinical studies have clearly demonstrated that inhaled corticosteroids could pose with ability of slowing down the progressive deterioration of lung functions and lead to the prolongation of life in broad population of patients with COPD. Benefit of treatment insists in decrease of frequency and severity of exacerbations, mildering symptoms, improving overall health state as well as exercise tolerance in patients with COPD. Clinical relevant is also reduction of the number of hospitalizations and mortality related to progression of COPD *(Tab. 2, Ref. 45)* Full Text (Free, PDF) *www.bmj.sk*.**
**Key words: chronic obstructive pulmonary disease, pharmacological treatment, inhaled corticosteroids.**

Chronic obstructive pulmonary disease (COPD) is one of the main causes of morbidity and mortality of the global population. In present, COPD is the 4th cause of death in U.S.A and 5th in the world (1). Epidemiologists of the World Health Organization (WHO) estimate, that disease prevalence ranges from 8 per 1000 inhibitants in developed countries to 25 per 1000 inhibitants in China (2). Incidence of COPD is probably substantially higher than health statistics indicate, because disease in great majority of patients is diagnosed as far as first acute exacerbation occurs or in progressive stage (3).

In the close decades we await further significant increase od prevalence and mortality associated with this disease. According to the data published by World Bank and WHO, the COPD will represent the 5th most frequent cause of morbidity (4) and moreover after 2020 the 3rd most frequent cause of death worldwide (5). In 2020, the prevention and treatment of COPD will represent 2nd item of expenses of burdening health care systems (4). Considering that, despite an undisputable progress, there is actually not pharmacological treatment evidently capable to modify the natural course of disease available so far.

Thanks gathering knowledge about pathophysiological mechanisms, a new therapeutic strategies become more real, especially on the field of pharmacotherapy. Recently, besides hot news in pharmacotherapeutic armamentary, the reevaluation according the role of inhaled corticosteroids in relationship to increasing evidence of their influence on the long term prognosis of patient is being performed. The outline of the stage treating managenment according GOLD initiative is presented in Table 1 (6).

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**Tab. 1. Treatment in various stages of COPD according GOLD initiative.**

| COPD Stages | 0: patients in risk of COPD | 1: mild COPD | 2: moderate COPD | 3: serious COPD | 4: very serious COPD |
|---|---|---|---|---|---|
| description | chronic symptoms, exposition to risk factors, normal spirometry | FEV1*/FVC** <70% FEV1 80% with or without symptoms | FEV1/FVC<70% 80%>FEV1>50% with or without symptoms | FEV1/FVC<70% 50%>FEV1>30% FEV1 with or without symptoms | FEV1/FVC<700% <30% or chronic respiratory failure or heart failure |
| | avoiding of risk factors, vaccination against ifluenza, education | | | | |
| | | add short acting bronchodilator when needed (e.g. SABA or/ and ipratropium), rehabilitation | | | |
| | | | add regular treatment with one or more long acting bronchodilators (ipratropium or LABA), inhaled corticosteroids after favourable therapeutic response | | |
| | | | | add inhaled corticosteroids, treatment of complications chronic respiratory failure | |
| | | | | | add long term oxygen treatment, consider surgery (volum-reducing intervention, lung transplantation |

* FEV1 – forced expiratory volume in 1 second, ** FVC – forced vital capacity

**Tab. 2. Inhaled and systemic corticosteroids*.**

| Systemic corticosteroids | | Inhalaled corticosteroids | |
|---|---|---|---|
| oral | parenteral | single | combined with LABA** |
| prednisone<br>metylprednisolone<br>triamcinolone<br>prednisolone<br>dexametasone | hydrocortisone<br>metylprednisolone<br>dexametasone | beclometasone<br>budesonide<br>fluticasone<br>propionate<br>mometasone<br>furoate<br>flunisolide<br>triamcinolone<br>dexamethasone | budesonide<br>+formoterol<br>fluticasone<br>propionate<br>+salmeterol |

* Review of available preparations regardless recommentadions in guidelines concerning the pharmacologic mamagement of COPD.
** LABA – long acting ß2 sympathomimetic drugs

**Recent view on the role of corticosteroids in the treatment of COPD**

Contrary to the treatment of bronchial asthma, where the role of corticosteroids has been cleared for the long time, evidence about their importance in the treatment of COPD has started to gather only recently. Pathophysiological studies in patients with COPD proved presense of chronic inflammatory process in bronchial wall and in lumen of peripheral airways with lost of elastic tissue structures and destruction of alveolar architecture (7). Coincidence of these alterations lead to an assumption, that corticosteroids could relieve inflammation by its powerful antiinflammatory effect and thus to improve lung functions. These anticipations have been reflected to frequent prescription if inhaled corticosteroids (ICS) for the patients with COPD despite of lack of scientific evidence of that time (8).

The detailed mechanism of the effect of corticosteroids in the treatment of COPD is not known. In the treatment of bronchial asthma, key role plays the ability of corticosteroids to decrease the number and activity of CD4+ T-lymphocytes through reduction of Th2 cytokins, reduction of number of dendritic cells as well as the total number of antigen presenting cells, normalization of apoptosis of neutrophils, decrease in bronchial hyperreactivity, stabilization of cell membranes, decrease of vessel permeability and vasodilation which is related to antiedematous effect (9). In the treatment of COPD could also be involved the ability of corticosteroids to inhibit transcription of the wide range of proinflammatory cytokins, suppression of the activation of adhesive molecules and

interference with eicosanoid synthesis at the supreme level, i.e. by inhibition of phospholipase A2. Modern ICS are able to decrease IL-8 (interleukine 8) production by inhibiting NF-$_k$B (nuclear factor $_k$B) and so to influence neutrofil inflammation (10). The weak point of ICS is the effect on particular neutrofil, but blockade of production of adhesive molecules for neutrofils like ICAM or E-selectin could approve their using (11). The overview of inhaled and systemic corticosteroids is shown is in Table 2.

*Inhaled corticosteroids*

Contrary to systemic corticosteroids essential for acute exacerbations of disease, the consensus according ICS usage has not been found yet (12). Several long-term, randomized, double blind clinical studies involving substantial part of patients suffering from COPD resulted in conclusion, that prolonged treatment with ICS (13–16), even in high doses (17) did mitigate the long term decline of FEV1 (forced expiratory volume in 1 second) in patients with COPD.

Studies differed in selection of patients with various degree of disease stage, proportion of active smokers, choice of particular ICS and it is dosage etc. Although during initial 6 months the FEV1 tended to decline more favourable in treated patients, consequently the curve of decrease converged with the group of untreated patients and after 3 years of follow up the values of FEV1 did not significantly change. Despite of following critical attidude, the latest metaanalyses of these long-term studies indicate that, ICS possess the ability to slow down the progressive worsining of lung funtions and to lead to prolongation of life in certain group of patients with COPD (18–20). Moreover, there is arising a question again whether ICS might power the natural progressive course of disease – hence ICS are lowering the rate of annual decline of FEV1 by 7.7 ml and more favourable effect can be achived by using the high dose regimens (decline by 9.9 ml/year) (18).

Reliable verified and till the most important benefit from the ICS treatment insists in decline of frequency and severity of exacerbations of the disease, in reducing symptoms and improving both health status and exercise tolerance in patients with COPD (12). The reduction of number of hospital admissions and of mortality related to progression of COPD is also of clinical relevance. The greatest benefit from ICS treatment probably have patients with advanced stage of disease (FEV1 <50 % of reference range, rapid decline in FEV1) with short history of smoking and asthma-like symptoms (21). Other analyses of long term studies revealed decrease of all cause mortality by 27 % compared with comparable effect in all stratified groups (according age, sex, body-mass index, baseline FEV1 value or smoking status) (22).

Therapeutical potential of ICS insist in supposed aditive effect by using in combination with inhaled long acting ß2 mimetics on lung functions a disease symptoms (23).

In patients with COPD the variability of therapeutic response to ICS could be related to involvement of asthmatic part in the COPD phenotype, where patients with asthmatic component response better to the treatment. Several national guidelines for the treatment of COPD recommended to make shortterm (lasting from 6 weeks to 3 months) therapeutic test in order to identify the patients with possible therapeutic benefit from ICS treatment. Nevertheless, short-term treatment with oral corticosteroids has low predictive value for longterm forecast of response to inhaled treatment (24). Therefore regular treatment with ICS is recommended particularly in symptomatic patients with verified response to ICS or in patients with FEV1 lower than 50 % of reference range (stage III and IV according GOLD) and with repeated exacerbations of disease requiring antibiotic treatment or systemic corticoid treatment (6). Anyway, based on results of recent metaanalyses we can await changes in therapeutic recommendations, which are substantiated with distinct benefits from ICS treatment also for patients with milder stages of COPD (18).

Several authors have pointed at the existence of withdrawal phenomenon after abrupt discontinuation of treatment at the end of last century. This phenomenon is associated with an increased risk of sooner onset of disease relaps and its severity as well as more profound decline od life quality indicators (25, 26). Similar results have been revealed also in latest studies concerning fluticasone withdrawal in patients treated with combination with salmeterol. Discontinuation of treatment with fluticasone resulted in rapid progression and further maintenance of deterioration of lung functions, stressing of breathlessness symptoms and increase of the number of disease exacerbations (27). Discontinuation of ICS treatment in patients with COPD requires carefull monitoring of clinical symptoms and functional respiratory indicators (12). Patients should not be exposed to undesired risk resulting from insufficiently considered treatment disruption from whichever reasons (including pharmacoeconomic).

*Corticoid resistence in COPD*

The main reason why the treatment with corticosteroids does not “work” so good like in bronchial asthma must be found in the difference between chronic inflammation in respiratory system by COPD from prevailing eozinophile asthmatic inflammation (28). Several studies pointed at the existence of “corticoid resistance” in COPD. Corticosteroids can inhibit the production chemotactic factor IL-8 by macrophages, but their influence on production of proteases participating on remodeling changes in airways – TNF-α (tumour necrosis factor alpha) and MMP-9 (matrix metaloproteinase 9) is insufficient (29). The cause should be impairment of activity of histonic deacetylase (HDAC) in macrophages in patients with COPD, which importance insists in deactivation of proinflammatory genes in cells like macrophages. HDAC impairment in patients with COPD can be caused not only by genetic factors but also by virus infections, oxidative stress or till now unknown noxes (30). Corticoid resistance of alveolar macrophages in patients with COPD could be reversed by theophylline treatment. The effect of theophylline seems to be independent from it is other pharmacological properties, i.e. inhibition of phosphodiesterase or influence on adenosine receptors. Theophylline is probably able to increase HDAC activity, which enables supression of expression of proinflammatory genes by corticoids (31). Probably there is similar effect medi-

ated through influence on HDAC activity also in ß2 sympathomimetics (32).

**Combined treatment with inhaled corticosteroids with long term ß2-sympathomimetics in COPD**

Experience from inhalation treatment of bronchial asthma indicates several positive interactions between long acting ß2-sympathomimetics (LABA) and ICS. ICS represents the key group of controllers in the treatment of bronchial asthma due to successfull suppression of asthmatic inflammation and decrease of bronchial hyperreactivity as well (9) and there is advancing experience with ICS treatment in COPD. Importance of LABA in bronchodilatory treatment of asthmatic patients and patients with COPD was verified for a long time, but thought their not bronchodilatory, "pleiotropic properties" also play a significant role in the treatment of persistent asthma and COPD (33).

Human gene for ß2-receptor contains on it's promotor sequence several sites where the regulatory effect of corticosteroids could be exerted through increase of transcription.

Long term treatment with ß2 sympathomimetics leads to decrease of activity of CREB (cyclic AMP response element binding protein) with consequent down-regulation of lung ß2-receptors due to limitation of expression in cells (34). Thus, through increase of transcription of ß2-receptor, corticosteroids have protective effect which is obvious also in epithelial cells of respiratory tract and bronchial smooth muscle cells. Therefore simultaneous administration of ß2 sympathomimetic and corticosteroid does not lead to substantial change in expression of ß2-receptors (35). In bronchial smooth muscle is the importance of this interaction questionable, though the benefit will be shown in preservation of non-bronchodilatory effects of ß2 sympathomimetics (33).

The relationship between ß2 sympathomimetics and activity of transcription factor CREB is getting forwards also in other circumstances. CREB has influence on variety of other transcription factors including glucocorticoid receptors (GR). Therefore theoretically high tissue concentrations of ß2 agonists might interfere with antiiflammatory effect of corticosteroids, although evidence about such not favourable interaction in human inflammatory cells is lacking. On the contrary, additive effect of corticosteroids and ß2 agonists on releasing of cytokines from human monocytes, which play very important role in the pathogenesis of inflammation in COPD, remains in combined treatment unaffected. The final impact of mentioned interactions is probable due to balance among number of number of GR, density of ß2 receptors, activity of CREB and presence of other proinflammatory cytokins. Thus it can differ from cell to cell in dependence on various conditions (36).

Synergic affect of combined treatment with corticosteroids and ß2 sympathomimetics is reciprocal and exceptional character of combining LABA and corticosteroids is due to unique mutual completing of their effects. LABA by acting through ß2 receptor enhances GR to binding with ICS and improved utilization of corticoid in cell core – by increasing of intranuclear localisation of GR and by stimulation of binding of GR to DNA. Molecular background of these interactions is probally stimulation of ß2 receptors, which leads to increase of intracellular cAMP and proteinkinase A concentrations with further phosphorylation of GR and other kinases. The final impact is the increase of gene transcription induced by corticosteroids and hence maintained proinflammatory effect (37). Salmeterol strengthens the inhibition of expression of intracellular adhesive molecules ICAM-1 induced by fluticasone. Also low doses of formeterol intensifies suppressive effect of budesonide on releasing GM--CSF (granulocyte-macrophage colony stimulating factor) from airway epithelium (32).

Inflammation in airways inactivates ß2 receptors with help of inflammatory chemokines (e.g. interleukine 1b), which lowers the response on ß2 sympatomimetics. The inactivation of ß2 receptor is due to an increased activity of G protein receptor kinase-2 (GRK-2) which phosphorylases the occupied ß2 receptor hence from interaction with GS protein. Corticosteroids supress the expression of GRK-2 and so prevent desensitisation of ß2 receptors. Another favourable interaction of corticosteroids with ß2 sympathomimetics results from the ability of corticosteroids to supress the transcription of gene from NK2 receptors, because that ß2 sympathomimetics can paradoxically contribute to bronchoconstriction by increase of expression of these receptors in bronchial smooth cells (32).

Complementary effects of ICS and LABA in vitro or in the treatment of asthmatics have focused the on the role of combined ICS plus LABA treatment also in COPD (38). Combined inhaled therapy becomes more frequent the subject of clinical trials researching awaited advantages from combination of fluticasone with salmeterol (28, 38, 39, 40), respective budesonide with formoterol (41).

By comparing combination of salmeterol/fluticasone with monotherapy or with placebo, as the most effective appeared to be the combined treatment after duration of one year. Although results from particular arms of study differed significantly in primary and some secondary endpoints, the overall benefit has been evaluated as limited (39). More favourable results have arised from another, 12 month study, where combination of salmeterol/ /fluticasone compared with monotherapy or placebo was also more effective in increase of FEV1 and decline of frequency of acute exacerbations and improving the quality of life as well (questionnaire SGRQ) (40). Favourable effect on functional and clinical indicators (dyspnea) starts in first days and majority of achieved improvements is obvious during first 2 weeks after iniciation of treatment (42).

Significant improvement of lung functions has been achieved by simultaneous administration of formoterol with budesonide and the effect lasted for the whole 12 month of study duration. In patients with moderate degree of COPD combined treatment led to reduction of frequency of serious exacerbations and exacerbations requiring systemic corticotherapy (41). Particularly exacerbations of disease markedly worsen the quality of life related with health status, accelerate the decline of lung functions and increase the mortality. Exacerbations and mortality are in very close relationship – mortality is increasing with frequency

of serious exacerbations, especially when hospital admission is required. Therefore, decrease of frequency of acute exacerbations might decrease related mortality as well. In present, the treatment with budesonide and formoterol in single inhalation device has been the only one combination ICS+LABA, which showed significant decrease the number of exacerbations in patients with COPD compared with LABA alone.

Results of multiple long term studies from the recent period concerning combined treatment ICS+LABA in COPD have brought encouraging, clinical relevant evidence of improvement (or preservation) of lung functions and improvement of life quality especially in patients with moderate and serious stage od disease. From that point of view, the the definitive results could be awaited after processing the data from till now largest, 3 year follow focusing at the effect of treatment salmeterol/fluticasone in single inhalation device on mortality, morbidity due to acute exacerbations and quality of life in patients with COPD. Preliminary results are indicating at reduction of mortality compared with placebo by 17 % (43).

Although combinations ICS+LABA is well established therapeutical option in patients with persistent bronchial asthma, the large population of patients with COPD benefits from such combination as well (44). This is the reason why recommendation of combined treatment ICS+LABA gradually enters to the guidelines for the management of COPD for patients with persisting clinical symptomatology in spite of monotherapy with bronchodilators (6, 45).

## Conclusion

Despite of increasing possibilities in the area of pharmacotherapy, the recent therapeutical management of COPD is not sufficient, which is also reflected into not favourable health statistics. Fortunately, close future opens new possibilies in the area of pharmacotherapy of COPD, where drug development runs quickly forwards. The interest focuses also on the efficacy of already established drug groups besides new ones, especially in the context with gathering knowledge and evidence leading to reevaluation on their position in the treatment of COPD. ICS is also one these drug groups. Recent data from well designed long-term clinical studies and their metaanalyses give enough reasons concerning their prescription for wider population of patients.

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