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Current trends in the asthma therapy

Asthma is a clinical syndrome characterized by recurrent episodes of airway obstruction that resolve spontaneously or as a result of treatment, which occurs in individuals who may periodically have normal airway function. The prominent symptoms of this disease include wheezing, breathlessness, chest tightness and cough. Airway narrowing results from a number of factors including thickening of the airway epithelium, the presence of liquids within the airway lumen, and an airway smooth muscle contraction. This inflammatory condition is a consequence of a chronic inflammatory disorder of the airways involving many cells, in particular mast cells, eosinophils, neutrophils, T-lymphocytes and the airway epithelium, with the participation of a number of mediators. The release of mediators from activated mast cells and eosinophils plays a major role in asthma. These processes are orchestrated by T-helper-2 lymphocytes (Th-2) through the actions of cytokines associated with the IL-4 gene cluster. The region of chromosome 5 contains the IL-4 gene cluster 5q 31-33 in which the allergic cytokines IL-3, IL-4, IL-5, IL-9 and IL-13 are encoded. The inheritance of certain alleles from this region are associated with a propensity toward an elevated Ig E response and the development of bronchial hyperresponsiveness. Although about 40 per cent of the clinical expression of an allergic disorder can be accounted for by genetic factors, but the expression of these genetic propensities is only realized through interaction with the common environmental allergens.

It has been suggested that the increased prevalence of asthma observed in many developed countries over the past thirty years is in part the result of a decrease in the incidence and severity of early childhood infections. Over the same period, there has been a decreased intake of dietary substances that contribute to antioxidant defence (antioxidants), and this appears to have contributed to the rise of asthma (2).

Since asthma is a chronic inflammatory illness, anti-inflammatory treatment is a cornerstone of the asthma therapy. Treatment with inhaled corticosteroids (ICS) improves the lung function, reduces asthma symptoms and the frequency and severity of asthma exacerbations. However, many patients with a more severe disease remain symptomatic on an ICS therapy despite taking inhaled corticosteroids only. For these patients therapeutic options include adding a long-acting β_2-agonist or increasing the dose of inhaled corticosteroid. It has been shown that addition of long-acting inhaled β_2-agonist to low- to medium-doses of inhaled corticosteroids is more effective than increasing the dose of ICS. The combination of long-acting β_2-agonist with an ICS provides improvement in the lung function and symptom control than at least doubling the dose of ICS, and it reduces the rate of exacerbations (1,3,4,7). The addition of long-acting inhaled β_2-agonists to ICS proves particularly beneficial in patients with moderate to severe persistent asthma. The clinical trials showed that in patients with moderately severe asthma, the addition of long-acting β_2-agonist to existing treatment allows the dose of ICS to be reduced

without loss of asthma control. Besides, a greater degree of asthma control may be achieved by adding a long-acting inhaled β_2-agonist to an unchanged dose of inhaled corticosteroid. In patients with mild persistent asthma taking low-dose corticosteroid, the addition of β_2-agonist improves asthma control and reduces the rate of severe asthma exacerbations more effectively than doubling the dose of corticosteroid.

These results suggest that a combined therapy with an ICS and long-acting β_2-agonist could be the reliance therapy for all patients with persistent asthma (4). Based on this current, national and international asthma management guidelines recommend the addition of long-acting β_2-agonists for chronic asthma that is at least moderately severe or mild asthma that is not well controlled with a low-dose inhaled corticosteroids. Attention was therefore focused on developing combination inhalers that included inhaled corticosteroids and long-acting β_2-agonists in order to simplify asthma treatment and improve adherence to prescribed medication (5). Two such combinations have been tested in asthmatic patients. These include salmeterol/ fluticasone (Seretide™, Advair™, Viani™ Glaxo Wellcome) and budesonide/ formoterol (Symbicort®, Astra-Zeneca) and such combinations have been shown in clinical studies to be very effective in controlling asthma. Studies also demonstrate that there are no physico-chemical interactions when the two medications are combined in a single inhaler. Salmeterol and formoterol are long-acting β_2-agonists, with duration of effect at least 12 hours. These drugs have some obvious pharmacological differences. The onset of action of formoterol is faster than that of salmeterol. Formoterol also has a high intrinsic activity. It has been shown in vitro in smooth muscle preparations and in vivo in asthmatic patients (7).

The clinical study has shown that salmeterol/fluticasone propionate combination therapy 50/250 μg twice daily (Seretide™, Advair™, Viani™ 50/250μg) in a single Diskus ™ inhaler is more effective in the treatment of moderate to severe asthma than a three-fold greater microgram dose of budesonide (800μg twice daily) in terms of improvement in the lung function and symptom control. These results support the complementary mechanism of action of long-acting β_2-agonists and inhaled corticosteroids and emphasize the value of combination therapy with these agents in the asthma therapy (3).

Another study has shown that in symptomatic patients with moderate-to-severe asthma, salmeterol/fluticasone propionate combination therapy 50/250 μg twice daily (Seretide™, Advair™, Viani™ 50/250μg) administered in a single convenient device (Diskus ™) was at least as effective as an approximately three-fold higher microgram corticosteroid dose of budesonide (800μg twice daily) given concurrently with formoterol (12μg twice daily) in terms of improvement in peak expiratory flow (PEV) and superior at reducing exacerbations at nights with symptoms or night-time awakenings. Salmeterol/fluticasone propionate was also the less costly treatment due primarily to lower hospitalization and dry costs (8).

It was also shown that those patients who received budesonide and formoterol in a single inhaler (Symbicort® Turbuhaler®) in comparison with the group receiving budesonide alone demonstrated significant improvements in the lung function. Budesonide/formoterol combination treatment also reduces the risk of asthma exacerbations (4). It was shown that budesonide/ formoterol (80/4.5 μg) combination therapy of asthmatic children twice daily after 12 weeks is more effective than an equivalent dose of budesonide 100 μg, twice inhalations twice daily. Relative to baseline, morning peak expiratory flow (PEV) increased to a significantly greater extent with budesonide/formoterol than with budesonide alone (7.22 % predicated normal vs. 3.45 % predicated normal). Evening peak expiratory flow (PEV) also increased significantly with budesonide/formoterol (6.13 % predicated normal vs. 2.73 % predicated normal). It means that budesonide/formoterol in a single inhaler provided rapid improvements in peak expiratory flow (PEV) and force expiratory volume in 1 second (FEV1) compared to inhaled budesonide alone (11).

It was also shown that budesonide/formoterol (160 / 4.5 μg twice daily) combination therapy of asthmatic patients, not controlled with inhaled glucocorticosteroids alone after 12

weeks is more effective than corresponding treatment with budesonide alone. There was greater increase in morning peak expiratory flow (PEF) with single inhaler (35.7 L· min^{-1}) and separate inhaler (32.0 L· min^{-1}) budesonide and formoterol compared with budesonide alone (0.2 L· min^{-1}). Similarly, evening PEF, use of rescue medication, total asthma symptoms scores and percentage of symptom-free days improved more with both single inhaler and separate inhaler therapy than with budesonide alone (12).

The same budesonide/ormoterol combination therapy was also effective in the long-term management of moderate to severe chronic obstructive pulmonary disease (COPD). Budesonide/formoterol reduced the mean number of severe exacerbations per patient per year by 24 % versus placebo and 23 % versus formoterol. FEV 1 increased by 15 % versus placebo and 9 % versus budesonide. Morning PEV improved significantly on day 1 versus placebo and budesonide. After 1 week, morning PEV was improved versus placebo, budesonide and formoterol. Improvements in morning and evening PEV versus comparators were maintained over 12 months. Budesonide/formoterol decreased all symptoms scores and use of reliever β_2-agonists significantly versus placebo and budesonide and improved a quality of life of asthmatic patients. Besides, the composition budesonide/formoterol was well tolerated (10).

Symbicort is registered as a maintenance treatment for asthma. This drug is indicated in the treatment of moderate and severe persistent asthma as well as in asthma which remains mild persistent the regular use of low doses inhaled corticosteroids alone. Symbicort rapidly reduces the symptoms of asthma and improves the lung function. Symbicort reduces the number of mild and severe exacerbations, when taken regularly over prolonged period (6,9,10,11,12).

The combination of budesonide/formoterol has a faster onset of bronchodilation than salmeterol/fluticasone. The rapid bronchodilatory properties of budesonide/formoterol suggest that this combination product leads to quick symptom relief and rapid normalization of airway calibre when such effects are required (7).

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SUMMARY

Asthma is a clinical syndrome recognized as chronic inflammatory condition of the airways that requires early pharmacological treatment and long-term management. Inhaled corticosteroids as anti-inflammatory agents are considered to be the first-line prophylactic treatment for patients with persistent asthma. For patients with a more severe disease and whose asthma is not fully controlled with daily dose of inhaled corticosteroid, therapeutic options advocate adding a long-acting inhaled β_2-agonist therapy, rather than an increase in the dose of inhaled corticosteroids. This therapeutic procedure improves the lung function and quality of life of asthmatic patients and reduces the number of exacerbations of asthma. Taking into account complementary effects and β_2-agonists of inhaled corticosteroids, the combination of these medicines in the same inhaler device has recently been introduced. Two such combinations: salmeterol/fluticasone (Seretide, Glaxo Wellcome) and budesonide/formoterol (Symbicort, Astra Zeneca) have been shown in clinical studies to be very effective in controlling asthma. It has been shown that budesonide/formoterol combination has a faster onset of bronchodilation than salmeterol/fluticasone.

Bieżące trendy w leczeniu astmy

Astma jest chronicznym stanem zapalnym dróg oddechowych, wymagającym wczesnej interwencji farmakologicznej i długotrwałego leczenia. U pacjentów przewlekle chorych na astmę stosuje się, jako leki przeciwzapalne, wziewne glikokortykosteroidy. U pacjentów, u których astma nie jest w pełni kontrolowana terapią glikokortykosteroidową, zaleca się stosowanie leczenia skojarzonego (podawanie długodziałającego β_2-agonisty łącznie z glikokortykosteroidem) zamiast zwiększania dawki samego glikokortykosteroidu. Tak prowadzona terapia doprowadza do usprawnienia wydolności oddechowej i poprawy ogólnego stanu pacjentów, a także zmniejsza częstotliwość napadów astmy. Ze względu na komplementarne działanie wziewnych glikokortykosteroidów i β_2-agonistów wprowadzono obecnie do lecznictwa preparaty złożone, zawierające te dwa składniki w tym samym inhalatorze. W leczeniu astmy bardzo efektywne okazały się połączenia salmeterolu z flutikazonem i budezonidu z formoterolem, przy czym połączenie budezonidu z formoterolem powoduje szybsze rozszerzenie oskrzeli niż połączenie salmeterolu z flutikazonem.