Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

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Authors' objectives
Background: In asthmatic patients inadequately controlled on inhaled corticosteroids and/or those with moderate persistent asthma, two main options are recommended: the combination of a long-acting inhaled ß2 agonist (LABA) with inhaled corticosteroids (ICS) or use of a higher dose of inhaled corticosteroids.

Objectives: To determine the effect of the combination of long-acting ß2 agonists and inhaled corticosteroids compared to a higher dose of inhaled corticosteroids on the risk of asthma exacerbations, pulmonary function and on other measures of asthma control, and to look for characteristics associated with greater benefit for either treatment option.

Search methods: We identified randomised controlled trials (RCTs) through electronic database searches (MEDLINE, EMBASE and CINAHL), bibliographies of RCTs, clinical trial registries and correspondence with manufacturers until May 2008.

Selection criteria: RCTs that compared the combination of inhaled LABA and ICS to a higher dose of inhaled corticosteroids, in children and adults with asthma.

Data collection and analysis: Two authors independently assessed methodological quality and extracted data. We obtained confirmation from the trialists when possible. The primary endpoint was the number of patients experiencing one or more asthma exacerbations requiring oral corticosteroids.

Main results: This review included 48 studies (15,155 participants including 1155 children and 14,000 adults). Participants were inadequately controlled on their current ICS regimen, experiencing ongoing symptoms and with generally moderate (FEV1 60% to 79% of predicted) airway obstruction. The studies tested the combination of salmeterol or formoterol with a median dose of 400 mcg/day of beclomethasone or equivalent (BDP-eq) compared to a median of 1000 mcg/day of BDP-eq, usually for 24 weeks or less. There was a statistically significantly lower risk of exacerbations requiring systemic corticosteroids in patients treated with LABA and ICS (RR 0.88, 95% CI 0.78 to 0.98, 27 studies, N = 10,578) from 11.45% to 10%, with a number needed to treat of 73 (median study duration: 12 weeks). The study results were dominated by adult studies; trial data from three paediatric studies showed a trend towards increased risk of rescue oral steroids (RR 1.24, 95% CI 0.58 to 2.66) and hospital admission (RR 2.21, 95% CI 0.74 to 6.64) associated with combination therapy. Overall, there was no statistically significant difference in the risk ratios for either hospital admission (RR 1.02, 95% CI 0.67 to 1.56) or serious adverse events (RR 1.12, 95% CI 0.91 to 1.37). The combination of LABA and ICS resulted in significantly greater but modest improvement from baseline in lung function, symptoms and rescue medication use than with higher ICS dose. Despite no significant group difference in the risk of overall adverse events (RR 0.99, 95% CI 0.95 to 1.03), there was an increase in the risk of tremor (RR 1.84, 95% CI 1.20 to 2.82) and a lower risk of oral thrush (RR 0.58, 95% CI 0.40 to 0.86) in the LABA and ICS compared to the higher ICS group. There was no significant difference in hoarseness or headache between the treatment groups. The rate of withdrawals due to poor asthma control favoured the combination of LABA and ICS (RR 0.65, 95% CI 0.51 to 0.83).

Authors’ conclusions: In adolescents and adults with sub-optimal control on low dose ICS monotherapy, the combination of LABA and ICS is modestly more effective in reducing the risk of exacerbations requiring oral corticosteroids than a higher dose of ICS. Combination therapy also led to modestly greater improvement in lung function, symptoms and use of rescue ß2 agonists and to fewer withdrawals due to poor asthma control than with a higher dose of inhaled corticosteroids. Apart from an increased rate of tremor and less oral candidiasis with combination therapy, the two options appear relatively safe in adults although adverse effects associated with long-term ICS treatment were seldom monitored. In children, combination therapy did not lead to a significant reduction, but rather a trend towards an increased risk, of oral steroid-treated exacerbations and hospital admissions. These trends raised concern about the safety of combination therapy in view of modest improvement in children under the age of 12 years.


Bibliographic details
Ducharme Francine M, Ni Chroinin Muireann, Greenstone Ilana, Lasserson Toby J. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma.
Cochrane Database of Systematic Reviews: Reviews 2010; Issue 4

AccessionNumber
10000005533
Date abstract record published
13/07/2012

Record Status
This is an abstract for a Cochrane review