How do we measure the effectiveness of inhaled corticosteroids in clinical studies?

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Summary
Inhaled corticosteroids (ICSs) are the gold standard anti-inflammatory therapy for asthma and have been studied using a variety of different clinical trial designs. In long-term comparative studies ICSs are more effective in controlling asthma than \( \beta \)-agonists or leukotriene antagonists (LTAs). Efficacy has also been shown retrospectively, as patients frequently experience an exacerbation of their asthma upon withdrawal of ICSs, whilst the regular use of low dose ICSs prevents death from asthma. The combination of ICSs with long-acting \( \beta_2 \)-agonists (LABAs) is effective for patients with asthma non-responsive to low doses of ICSs, particularly in reducing exacerbations. In shorter term studies a modest dose–response effect of ICSs has been shown for lung function, symptom control and oral corticosteroid use in asthmatic patients. ICSs are also effective in reducing airway hyperresponsiveness (AHR) to various stimuli, as well as reducing exhaled nitric oxide (NO) concentrations and the number and activation state of a wide variety of inflammatory cells. Finally, using allergen challenge models even single doses of ICSs have profound inhibitory effects on the late asthmatic reaction. Since ICSs are the mainstay of asthma management guidelines, it is important that novel therapies should be judged against ICSs in future clinical trials. There are many potential designs for these comparative studies.

Introduction

Inhaled corticosteroids (ICSs) are recommend as first line therapy for all asthmatic patients with persistent symptoms and are the most effective therapy currently available for the treatment of asthma. They have revolutionised asthma treatment and have become the mainstay of therapy for patients with chronic disease. Clinically, ICSs are very effective in controlling asthma symptoms in
patients of all ages and severity. They improve lung function and quality of life, reduce the frequency of exacerbations and may prevent irreversible airway changes. The effectiveness of corticosteroids is based on the fact that they have a wide spectrum of anti-inflammatory action, reducing the number and activation state of many cells involved in the underlying inflammation of asthma. The aim of this review is to assess the various clinical trial designs used to determine the efficacy of ICSs in asthma.

Comparative studies

A simple way to assess the efficacy of ICSs is to compare their effect(s) with other agents commonly prescribed to treat asthma. In the following section the efficacy of ICSs is compared to that of inhaled $\beta_2$-agonists, or leukotriene antagonists (LTAs).

**Inhaled corticosteroid versus inhaled $\beta_2$-agonist**

Haahkela and colleagues\(^1\) compared the effect of an ICS, budesonide (600 $\mu$g bd), and an inhaled $\beta_2$-agonist, terbutaline (375 $\mu$g bd), in the long-term management (2 years) of patients with newly detected asthma (n = 103). The study showed that budesonide was more effective than terbutaline in improving airway hyperresponsiveness (AHR) to histamine and improving morning and evening peak expiratory flow (PEF) (Fig. 1), and more effective in reducing asthma symptoms and use of rescue medication.\(^1\) A follow-up biopsy study of 3 months duration using the same concentrations of budesonide and terbutaline in 14 patients with newly diagnosed asthma showed that budesonide was more effective than terbutaline in ameliorating abnormalities of the bronchial epithelium and decreasing inflammation in the airways.\(^2\) In particular, patients treated with budesonide had increased numbers of ciliated airway cells and intraepithelial nerves, as well as fewer inflammatory cells (including eosinophils) especially in the epithelium.\(^2\)

**Inhaled corticosteroid versus leukotriene antagonist**

Bukstein and colleagues\(^3\) evaluated the efficacy of oral montelukast and inhaled fluticasone propionate (FP) in a randomised, prospective 12-month 'real-world' observational analysis of children (6–15 years) with mild persistent asthma. The results of this study suggested that oral montelukast and inhaled FP have similar 'real-world' efficacies in the treatment of these patients, possibly as a result of the significantly better adherence to oral montelukast therapy. In general, ICS are much more effective than LTAs in asthma trials, ICS usually causing about double the improvement in lung function than found with LTAs. However, in adults with persistent asthma, long-term treatment with low dose FP was more effective than oral montelukast as first-line maintenance therapy.\(^4,5\) Similarly, in a short-term study, steroid-naive patients with moderate asthma treated with either montelukast (10 mg, once a day) or low-dose inhaled FP (100 $\mu$g bd) had comparable bronchodilator action, but those treated with FP showed additional attenuation of airway inflammation as evidenced by reduced exhaled nitric oxide (NO) and eosinophils in induced sputum.\(^6\)

**Additive therapy**

The efficacy of ICSs can be observed when added to another agent used to treat asthma. Results from clinical studies using non-fixed combinations of ICSs and LABAs (i.e. delivered via separate inhalers) have demonstrated that the addition of a long-acting $\beta_2$-agonist (LABA) to an ICS is associated with statistically and clinically significant improvements in both objective and subjective measures of asthma control relative to the administration of higher doses of ICS.\(^7,8\) Results from a systematic review\(^9\) showed that the addition of salmeterol in patients taking low-to-moderate doses of ICSs gave improved lung function (PEF and FEV\(_1\)) and increased the number of days and nights without symptoms or need for rescue treatment with no...
increase in exacerbations of any severity. Similarly, a one year study in 852 patients with asthma showed that the addition of formoterol (12 µg) to budesonide (100 or 400 µg) caused a dose-dependent reduction in the rate of both mild and severe exacerbations compared to budesonide alone. Combination therapy with salmeterol and ICSs in patients with persistent asthma provided significantly greater improvement in overall asthma control than oral zafirlukast or oral montelukast therapy.

ICSs and LABAs are also available as a combination product delivered by a single inhaler at fixed dosages. Although, ICS/LABA combinations suit selected asthmatic patients, the fixed-dose nature of the combination reduces the flexibility of treatment and challenges the step care approach advocated by current National Institutes of Health (NIH) guidelines. It is essential that medication can be easily added and dosages of controller medication increased as disease severity increases. Conversely, once symptoms subside the step care approach recommends gradual reduction of controller medication dose and cessation of add-on therapies. Non-fixed combination products provide physicians and patients with greater flexibility.

Steroid tapering

Discontinuation of corticosteroid therapy allows the retrospective examination of ICS efficacy in asthmatic patients. In a follow up study to their 1991 study, Hahtela and colleagues showed that early treatment with inhaled budesonide resulted in long-lasting control of mild asthma. Maintenance therapy could be given at a reduced dose (400 µg/day), but discontinuation of treatment was often accompanied by exacerbation of the disease. Patients who discontinued budesonide treatment had a reduced PEF (Fig. 2) and forced expiratory volume in one second (FEV₁) and increased AHR to histamine.

In another study, a group of 10 patients with stable asthma underwent a gradual reduction in ICS daily dose by 200 µg at weekly intervals. Each patient developed an exacerbation of symptoms on average 16 days after the onset of steroid reduction. This loss of asthma control was accompanied by a deterioration in FEV₁, PEF and an increase in AHR and the number of circulating eosinophils. The deterioration in daily symptom score preceded changes in PEF. Increasing the steroid dose induced a reversal of each of these changes. Some patients are more at risk of exacerbation than others following a reduction in ICSs. Using a Kaplan–Meier survival analysis Leuppi and colleagues showed that predictive markers of asthma exacerbation during a stepwise dose reduction of ICS were AHR to both histamine and mannitol at baseline; AHR to mannitol during the dose-reduction phase; patients >40 years; and % sputum eosinophils.

Mortality

Assessment of mortality is a relatively crude way to assess the efficacy of ICSs in asthma and prospective studies are almost impossible to conduct. However, in a retrospective study Suissa and colleagues used the Saskatchewan Health database to form a population-based cohort of all patients aged 5–44 years who used anti-asthma drugs during the period 1975 to 1991. On the basis of a continuous dose–response analysis they...
calculated that the rate of death from asthma decreased by 21% with each additional canister of ICS used in the previous year. In addition, the rate of death from asthma during the first three months after discontinuation of ICSs was higher compared with those patients who continued treatment.\(^\text{16}\)

Dose–response studies

The aim of dose–response studies is to show an increasing effect from low to high doses. There is little evidence to show that the effects of ICSs are dose-dependant, as they tend to have a fairly flat dose–response curve. Large numbers of patients are required to show any dose–response with ICSs. It is also worth noting that the shape of the dose–response curve will vary according to the severity of asthma. Milder asthmatic patients should be well controlled on low doses of ICSs.

Budesonide

A 12 week study in 473 patients with chronic asthma treated with budesonide showed a statistically significant dose–response effect for the mean change from baseline for both morning PEF (Fig. 3) and FEV\(_1\).\(^\text{17}\) However, very little improvement was noted upon doubling the dose of budesonide from 800 to 1600 \(\mu\)g. Budesonide-treated patients also demonstrated significant reduction in asthma symptoms and bronchodilator use compared with placebo.\(^\text{17}\)

Markers of inflammation

In patients with asthma the efficacy of ICSs in improving lung function and symptoms and reducing the frequency of exacerbations is well-documented. However, the efficacy of corticosteroids can also be shown by examining their anti-inflammatory effect(s). The anti-inflammatory effect(s) of corticosteroids is usually examined using invasive sampling methods such as bronchoalveolar lavage and bronchial biopsies, but induced sputum and nasal lavage have also been used.

Eosinophils

According to management guidelines the dose of ICSs is determined according to lung function and symptoms. However, a management strategy based on normalisation of eosinophilic inflammation has recently been proposed.\(^\text{18}\) In a group of patients with moderate-to-severe asthma (\(n = 74\)) the sputum eosinophil count was 63\% lower and the incidence of both severe asthma exacerbations and hospital admissions were significantly lower in the sputum management group than in the standard management group.\(^\text{18}\) These benefits were achieved without the need for additional anti-inflammatory treatment.

Taylor and colleagues\(^\text{19}\) investigated the effects of 14 days treatment with three doses of the novel corticosteroid ciclesonide (50, 200 and 800 \(\mu\)g) twice daily on inflammatory mediators in induced sputum and AHR to adenosine monophosphate (AMP) in 29 patients with mild-to-moderate allergic asthma. Results showed a reduction in the number of eosinophils and the concentration of eosinophilic cationic protein in induced sputum and a dose-dependent reduction in AHR to AMP.\(^\text{19}\) These results indicate that in patients with mild-to-moderate asthma, assessment of AHR to AMP may be a more sensitive method to evaluate a dose–response relationship of an ICS than inflammatory parameters in induced sputum.

Nitric oxide

NO is an exhaled marker of inflammation and oxidative stress in asthma. Lim and colleagues\(^\text{20}\) showed that four weeks treatment with inhaled budesonide (800 \(\mu\)g bd) significantly reduced the concentration of NO in the exhaled air of 14 mild asthmatic patients with a concomitant improvement in FEV\(_1\) and AHR, and a reduction in the number of sputum and biopsy eosinophils. Similarly, Kharitonov and colleagues\(^\text{21}\) showed a dose-dependent speed of

![Figure 3 Budesonide dose–response curve: effect of budesonide on morning peak expiratory flow (PEF) in patients with chronic asthma \((n = 473)\). Reprinted with permission from Busse et al.\(^\text{17}\)](image-url)
onset and cessation of action of budesonide on exhaled NO and asthma symptoms in a parallel group study in 28 mild asthmatic patients over 3 weeks. Treatment with 400 μg/day budesonide reduced exhaled NO faster than 100 μg/day and resulted in faster recovery of exhaled NO after treatment cessation.21

Allergen challenge

Allergen challenge studies are a good way of examining the effect of a single dose of ICS. After allergen challenge the early asthmatic response occurs between 0 and 2 h and is associated with mast cell degranulation. The last asthmatic response involves the recruitment of numerous inflammatory cells and occurs 4–10 h post allergen challenge. Parameswaran and colleagues22 compared the protective effects of single and regular doses of inhaled FP with single and regular placebo doses on early and late asthmatic responses. They discovered that a single dose of FP (250 μg) given 30 min before allergen challenge was just as effective as regular treatment for two weeks (250 μg bd) in affording protection against the early and late asthmatic response, increased AHR and sputum eosinophilia (Fig. 4).22 Mild asthmatics treated for 6 days with MF also demonstrated attenuation of allergen-induced early and late responses, AHR and sputum eosinophilia.23 A reduction in airway responsiveness to inhaled AMP has recently been shown within 2 h of a single inhalation of FP (100, 250 or 1000 μg) suggesting a rapid topical anti-inflammatory action.24 Similarly, Gibson and colleagues25 showed that in adults with stable asthma (n = 41) a single dose of budesonide (2400 μg) significantly reduced the number of sputum eosinophils and induced a 2.2-fold improvement in airway responsiveness to hypertonic saline 6 h after treatment. Finally, patients with mild allergic asthma treated for 1 week with ciclesonide (800 μg bd) had a significantly reduced early and late asthma response compared to placebo.26

Nasal lavage model

There are considerable problems when investigating immunological events that are taking place in the lungs. Bronchial biopsy, bronchoalveolar lavage, and even sputum induction all have problems with accessibility and invasiveness. By contrast, the nasal passages are easily accessible. With the nasal lavage model, test agents are delivered to the nasal mucosa by means of a spray which accurately administers substances to the nose in small volumes. The patient leans forwards, and after allergen challenge (e.g. with grass pollen) the nose is rinsed with warm phosphate buffered saline (Fig. 5). Surface exudations/secretions from the nasal mucosa are effectively sampled and collected onto filter paper. Samples obtained from the nasal passages can then be analysed via cytometric ELISA using a Luminex system. Using this system, Ed Erin and colleagues (data on file) showed that following allergen challenge, interleukin (IL)-4, IL5 and IL13 were elevated in nasal secretions. The highest concentration of these TH2 cytokines occurred 6–8 h post-allergen challenge. Pre-treatment with a single dose of budesonide (200 μg) completely ablated these responses (Fig. 6).

Conclusion

This review examined the efficacy of ICSs in a variety of ways. Firstly, in long-term studies (usually 1–3 years duration) comparing the efficacy of ICSs with other agents (i.e. β-agonists or LTAs), assessing the efficacy of ICS/LABA combinations, determining the effect of discontinuing corticosteroid therapy and determining the risk of mortality; secondly in studies of shorter duration (usually 12 weeks), by examining the dose–response of different ICSs; and finally by reviewing the effect of single doses of corticosteroids on allergen challenge in a number of models. The results of these studies show that ICSs are very effective in reducing the signs and symptoms of asthma as well as the underlying inflammatory component of the disease. In the future, the challenge will be to
develop therapy that can either be added on or used as an alternative to ICSs.

References


![Figure 5 Nasal lavage model.](image-url)

