The treatment of chronic asthma in children under the age of 12 years

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years

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Executive summary

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Executive summary

Current asthma management

Various strategies are used in the prevention and management of asthma. Pharmacological management includes, among other drugs, inhaled corticosteroids (ICS) and short- and long-acting beta$_2$ agonists (SABAs/LABAs). Both ICS and LABAs are inhaled controller medications that need to be taken on a long-term daily basis for maximum symptom control. The medications can be delivered via a number of different types of inhaler devices; these differ in the efficiency with which they deliver the drug to the lower respiratory tract.

There are currently three ICS available as licensed preparations for children aged under 12 years: beclometasone dipropionate (BDP), budesonide (BUD) and fluticasone propionate (FP). Two of the ICS are available as licensed preparations in combination with LABA: FP used in combination with salmeterol (SAL) and BUD used in combination with formoterol fumarate (FF).

Objectives

The aims of this health technology assessment are:

- to identify, appraise and synthesise, where appropriate, the current evidence base on the clinical effectiveness and cost-effectiveness of ICS alone and ICS used in combination with a LABA in the treatment of chronic asthma in children aged under 12 years
- to identify the costs associated with the different treatments
- to provide estimates of cost-effectiveness, where possible, of the different treatment options.

An accompanying health technology assessment has been conducted in adults and children over 12 years.

Methods

The assessment was conducted within the context of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) Guideline on the management of asthma.

The assessment comprises a systematic review of clinical and cost-effectiveness studies and economic analyses.

For the assessment of clinical effectiveness, a literature search was conducted on a number of electronic bibliographic databases (e.g. MEDLINE, Cochrane CENTRAL and EMBASE) up to February/March 2006 (and updated again in October 2006). Systematic reviews and randomised controlled trials (RCTs) were included. Only trials testing different drugs using the same inhaler device/propellant were included. Therefore, trials testing, for example, BDP via a pressurised metered dose inhaler (pMDI) versus BUD via a dry powder inhaler (DPI) were excluded, as were trials testing, for example, BDP via hydrofluoroalkane (HFA)-propelled pMDI versus BUD via chlorofluorocarbon (CFC)-propelled pMDI. The scope of the review was to consider the effectiveness of the inhaled steroids, as opposed to their delivery devices. Some clinical trials were specifically designed to evaluate device effects using clinically inequivalent doses. These were therefore excluded to reduce the likelihood of confounding.

A flexible framework was used to allow different types of economic analyses and a cost comparison or a cost–consequence comparison was conducted for each review question identified.

Results

Clinical effectiveness review

Of 5175 records identified through systematic literature searching, 34 records describing 25 studies were included. Of these, 16 were fully published RCTs, six were systematic reviews, and three were post-2004 conference abstracts.

Noticeably absent from the evidence base are studies in children and infants aged under 4 years.

The most frequently reported relevant outcomes in the 16 RCTs were PEF (13 trials), FEV_1 (13 trials), symptoms (13 trials), adverse events or exacerbations (13 trials), use of rescue medication (12 trials), markers of adrenal function (e.g. blood or urine cortisol concentrations) (13 trials), ▶

height and/or growth rate (seven trials) and markers of bone metabolism (two trials). The detail of reporting outcomes varied considerably among the studies.

ICS versus ICS

Five RCTs were identified that compared the three ICS with each other at low doses (200–400 µg BDP/day or equivalent) and seven comparing them at high doses (800–2000 µg BDP/day or equivalent). No consistent significant differences or patterns in differential treatment effect among the outcomes were evident when single ICS were compared with each other at either low or high doses at the accepted clinically equivalent doses. Where differences were statistically significant at high doses, such as for lung function [e.g. forced expiratory volume in 1 second (FEV_1) and growth], they favoured FP, but this was generally in studies that did not compare the ICS at the accepted clinically equivalent doses. Differences between the drugs in impact on adrenal suppression were only significant in two studies. Occurrence of adverse events appeared similar.

ICS versus ICS/LABA

Only one trial was identified that compared ICS at a higher dose with ICS and LABA in combination. It included a relatively small proportion (~12%) of children and reported only growth rate and adrenal function for the child cohort. Growth rate significantly favoured the combination inhaler (FP/SAL) whereas no significant difference in adrenal function between ICS monotherapy (FP) and the combination inhaler was observed.

The overall trial results (including adults) significantly favoured combination therapy in prolonging the time to first severe and mild exacerbation compared with ICS alone. Furthermore, combination treatment was significantly associated with reduced reliever medication use, improvements in measures of lung function and the number of night-time awakenings relative to monotherapy.

Two large, multi-centre trials were identified that compared ICS at the same dose with ICS and LABA in combination. In both trials most outcomes numerically favoured the combination inhaler (either FP/SAL compared against FP or BUD/FF compared against BUD). However, in one of the studies (FP/SAL), it is unclear whether any of the differences were statistically significant, and in the other study (BUD/FF) only lung function outcomes differed significantly.

ICS/LABA versus ICS/LABA

Only one trial was identified that compared combination inhalers with the same drugs delivered in separate inhalers. There were no statistically significant differences in measures of lung function between the two treatment regimens. The mean difference in the morning PEF was within a defined range for clinical equivalence.

No trials have so far been conducted in children to compare the clinical effectiveness of the two combination inhalers.

Economic analysis

Results

ICS versus ICS

A cost comparison was undertaken to compare the costs of ICS at the starting low dose of 200 µg/day, the maximum low dose of 400 µg/day and the assumed median 'high-level' daily dose of 800 µg/day (all BDP–CFC equivalent doses).

At daily doses of 200 µg (BDP–CFC equivalent)/day, CFC-propelled BDP appears to be the current cheapest ICS product. If CFC-propelled products are excluded from the available products, BDP is still usually the cheapest but at a higher annual cost. At doses of 400 µg/day, BDP remains the cheapest ICS product available both with the inclusion and exclusion of CFC-propelled products, although the cost differences between products are smaller when CFC-propelled products are excluded.

On average, at doses of 800 µg (BDP–CFC equivalent)/day, although BDP is the current cheapest ICS product with both the inclusion and exclusion of CFC-propelled products, it is only slightly cheaper than BUD or FP. However, although the use of weighted averages provides a useful way to compare the mean annual cost between the different ICS, at all dose levels it disguises the often large cost differences between the different preparations of each ICS.

ICS versus ICS/LABA

Only the combination inhaler, Seretide Evohaler, is slightly cheaper than the weighted mean cost of all types of ICS at increased dose except BDP 400 µg/day (including CFC-propelled products). Both the combination inhalers, Seretide Accuhaler and Symbicort Turbohaler, are more expensive than the weighted mean cost for all types of ICS at a two-fold increased dose. Compared with the lowest cost preparation for each ICS drug, all the combination inhalers are always more expensive than the ICS products at increased dose. ▶

ICS/LABA versus ICS/LABA
Taking either FP in combination with SAL (Seretide Evohaler or Seretide Accuhaler) or BUD in combination with FF (Symbicort Turbohaler) is cheaper than taking the relevant ingredient drugs in separate inhalers.

Based on a comparison of the costs only, BUD in combination with FF (Symbicort Turbohaler) is more expensive than both the FP/SAL (Seretide Evohaler or Seretide Accuhaler) combination drugs currently available.

Discussion

Limitations of the evidence base

This review identified very few trials including children under the age of 12 years and none including children under the age of 5 years. The methodological quality of the included RCTs varied considerably, and there was considerable variation in the way in which outcomes were defined, measured and reported across the included trials. This variety of definitions makes it difficult to compare the therapeutic activity of the different interventions between the trials, and in this instance makes combining studies in a meta-analysis inappropriate.

The aim of the trials varied considerably, with some primarily assessing safety and others primarily evaluating efficacy. The included trials also varied in treatment duration from around 6 weeks to 20 months, with the majority lasting 12 weeks. These trials therefore do not adequately capture the longer term effects of ICS and LABA therapy, particularly long-term adverse events and the impact on growth. Additionally, in the majority of trials it was not clear what constituted the minimum clinically significant change for many of the reported outcomes, such as lung function, symptoms or exacerbations.

The two other issues that have not formally been assessed in this report are considerations of the type of inhaler device and concordance, factors that are inextricably linked. It is well recognised that a large proportion of the asthmatic population has difficulty in using particular inhaler devices. This difficulty relates particularly to pMDIs and to a less extent to DPIs. Both require the ability to coordinate the inhalation with activation of the device. For paediatric populations, the use of a pMDI is usually combined with a large volume spacer. However, within the context of a clinical trial, only those patients who are able to use the type of device under evaluation effectively will be eligible for inclusion in the trial. Evidence for the effectiveness of inhaled corticosteroids and beta$_2$ agonists for asthma from clinical trials should therefore be considered carefully for its generalisability to the typical population with asthma, as opposed to the subgroup of patients selected for their ability to use the inhaler effectively. Furthermore, given the probable device-related variations in both compliance with correct inhaler technique and adherence to recommended daily doses, the rate of concordance with treatment regimens is likely to be considerably higher in clinical trials than in routine practice.

ICS versus ICS

When evaluated in pair-wise comparisons, there were few statistically significant differences between the three ICS comparators at both low and high dose. However, although there were no clear significant differences in treatment effects between the comparators, they cannot necessarily be assumed to be equivalent. Rather, there is a lack of evidence of differential effectiveness from the trial evidence available, rather than evidence of equivalence.

At all doses of ICS licensed for use in children, BDP, both including and excluding CFC-propelled products, is the cheapest ICS currently available. When non-CFC-propelled products only are considered, the mean annual cost of ICS therapy increases for all three ICS, but the overall cost differences between the drugs diminish.

ICS versus ICS/LABA

There is very limited evidence available for the comparative efficacy and safety of ICS and LABAs in children. Where significant differences between ICS compared with ICS and LABA have been identified, they have favoured the latter. Based on costs only, the extra annual cost of combination therapy versus an increased dose of ICS alone varies enormously, depending on the exact ICS preparation used. On the whole, only Seretide Evohaler is slightly cheaper than the weighted mean cost of all types of ICS, except BDP. However, the combination inhalers are always more expensive than the lowest cost preparation of each ICS drug at increased dose.

Use of a combination inhaler is always cheaper than taking the same ingredient drugs in separate inhalers. At the present time, the combination inhaler containing FP/SAL is cheaper than combinations containing BUD/FF. However, ▶

these combination products have not been compared in direct head-to-head trials, and therefore differences in clinical effects cannot be ruled out.

Conclusions

The limited evidence available indicates that there are no consistent significant differences in effectiveness between the three ICS licensed for use in children at either low or high dose. BDP CFC-propelled products are often the cheapest ICS currently available at both low and high dose, and may remain so even when CFC-propelled products are excluded. Exclusion of CFC-propelled products increases the mean annual cost of all BUD and BDP, while the overall cost differences between the comparators diminish.

There is very limited evidence available for the efficacy and safety of ICS and LABAs in children. From this limited evidence, there appear to be no significant clinical differences in effects between the use of a combination inhaler versus the same drugs in separate inhalers. There is a lack of evidence comparing ICS at a higher dose with ICS and LABA in combination and comparing the combination products with each other.

In the absence of any evidence concerning the effectiveness of ICS at higher dose with ICS and LABA, a cost–consequence analysis gives mixed results.

There are potential cost savings to the NHS with the use of combination inhalers compared to separate inhalers. At present prices, the BUD/FF combination is more expensive than those containing FP/SAL, but it is not known whether there are clinically significant differences between them.

Research recommendations

A scoping review is required to assess the requirements for additional primary research on the clinical effectiveness of treatment for asthma in children under 5 years old. Such a review could also usefully include all treatment options, pharmacological and non-pharmacological, for asthma.

There is currently no trial evidence available to inform the relative effectiveness of the two combination inhalers of FP/SAL and BUD/FF within a paediatric population. The results of the current assessment suggest that for FP/SAL there are no significant differences in effectiveness in terms of whether the drugs are delivered in a single inhaler or concurrently in two separate inhalers. However, as ease of treatment regimen may potentially affect concordance then a direct head-to-head trial that compares the two combination therapies of FP/SAL and BUD/FF is warranted.

Given the chronic nature of asthma and that treatment may be necessary on a long-term basis from childhood, it is important to assess whether the addition of a LABA to a lower dose of ICS could potentially be as effective as an increased dose of ICS alone, but also be steroid sparing.

There is a need for the long-term adverse events associated with ICS use to be assessed systematically. Initial searches undertaken for this assessment indicate that there are at present no good-quality systematic reviews available that have assessed all potential long-term adverse events associated with the three different ICS comparators. Future reviews should aim to examine studies of longer term follow-up and use appropriate data sources such as cohort and case–control studies and registry data where available.

Future trials of treatment for chronic asthma in children should aim to standardise further the way in which outcome measures are defined. There should be a greater focus on patient-centred outcomes such as HRQoL and symptoms. This will provide a more meaningful estimation of the impact of treatment on asthma control. Methods of reporting also require standardisation.

Publication

Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years. *Health Technol Assess* 2008;**12**(20).

NIHR Health Technology Assessment Programme

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