Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of budesonide (Pulmicort Turbohaler; AstraZeneca), once daily, for the treatment of mild persistent asthma. The dose was 200 microg for children aged younger than 11 years and 400 microg for other patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who had been diagnosed with mild persistent asthma 2 years or less before randomisation. The patients were diagnosed according to symptom scores (at least one symptom, such as wheeze, cough and chest tightness over one week, but not as often as every day during the 3 months preceding the initial visit) and airway reversibility. Patients with significant co-morbidity were excluded.

Setting
The setting was primary care. The economic study was conducted in the USA.

Dates to which data relate
The dates during which effectiveness and resource use data were gathered were not reported. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Sample size calculations were conducted. These suggested that the group of patients enrolled in the study provided a 95% power at a significance level of 5% to detect a 35% reduction in the risk of emergency treatment or hospitalisation. Of the 7,241 patients who entered the study, 56 patients (from 4 centres) were discarded for administrative reasons and 20 patients did not receive the study drug. Therefore, the final sample comprised 7,165 patients, 3,597 in the budesonide group and 2,568 in the control group. In the budesonide group, the mean age of the patients was 23.7 (+/- 14.6) years and 54.2% were female. In the control group, the mean age was 24.3 (+/- 14.8) years and 54% were female.
Study design
This was a randomised, double-blind clinical trial that was conducted in several centres in 32 countries. The methods of randomisation and blinding were not reported. The patients were followed for 3 years and 5,155 patients were lost to follow-up. A total of 336 patients dropped out before the first efficacy assessment. The dropout rate and reasons for discontinuation were comparable between the groups. The patients were seen at weeks 6 and 12, and then every 3 months thereafter (a total of 14 visits). The symptoms were estimated on a basis of 2-week recall at every visit.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcome used was the number of symptom-free days (SFDs). This was defined as a complete 24-hour period with no asthma symptoms. The study groups were comparable at baseline in terms of their demographics and disease characteristics. The analysis of effectiveness was performed on the whole sample as well as on 3 sub-groups of patients defined according to age classes. The three sub-groups were those between 5 and 10 years (children), those between 11 and 17 years (adolescents), and those of 18 years or older (adults).

Effectiveness results
Significantly fewer SFDs were reported in budesonide patients then in those who received usual care.

The reduction in SFDs was 14.1 (+/- 1.3) per year in the whole sample, 5.6 for children, 8.9 for adolescents and 20 for adults.

These differences between budesonide and usual care were statistically significant for all age groups, (p<0.001).

Clinical conclusions
The effectiveness results showed that budesonide was effective in reducing days with asthma symptoms in comparison with usual care.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was the number of SFDs. This was obtained directly from the effectiveness study. The SFDs were discounted at an annual rate of 3%.

Direct costs
A discount rate of 3% was used since the costs were incurred during 3 years. The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were budesonide, hospital days, emergency department visits, physician or nurse visits, telephone calls and concomitant asthma-related medications. Medications not strictly related to asthma treatment were not considered. The cost/resource boundary of the health care system was adopted. Resource use was estimated using actual data derived from the sample of patients used in the effectiveness study. The costs reflected actual reimbursement rates observed in the USA. They were estimated from a large medical and pharmacy claims database, which covered more than 16 million managed-care lives, thus representing typical US costs. The drug costs were estimated from wholesale prices, which were reduced by 15% to approximate true acquisition costs. Standard daily dosages were assumed for each patient. The price year was 1999.

Statistical analysis of costs
Wilcoxon and z tests were conducted to test the statistical significance of differences between the groups in the costs and resources used. The costs were log-transformed assuming a bivariate normal distribution, as the costs were positively skewed and heteroskedastic. Linear regression analyses were carried out on the costs, as well as the SFDs. The covariates used were gross national product per capita, gender, smoking status, prebronchodilator forced expiratory volume as a percentage of predicted normal values, and the percentage of SFDs.
Indirect Costs
Indirect costs (i.e. productivity losses and absences from school) were included for the societal perspective. The unit costs and the quantities of resources used were presented separately. The costs were discounted using an annual rate of 3%. Resource use was estimated using data derived from the sample of patients who were included in the clinical trial. Productivity losses were obtained using the human capital approach, while absences from school were estimated using the daily wage rate of the caregiver. The costs were estimated from data referring to the US workforce. The price year was 1999.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were conducted to address with variability in the data. The variables investigated were the discount rate and unit costs.

Estimated benefits used in the economic analysis
The discounted SFDs over the 3-year period were:
895 (+/- 2.8) with usual care and 935 (+/- 2.4) with budesonide in the whole sample;
948 (+/- 3.4) and 964 (+/- 3.2) in the group of children;
928 (+/- 5.6) and 953 (+/- 5) in the group of adolescents; and
858 (+/- 4.4) and 916 (+/- 3.7) in the group of adults.

Cost results
The discounted direct costs over the 3-year period were:
$1,360 (+/- 32) with usual care and $1,818 (+/- 23) with budesonide in the whole sample;
$1,347 (+/- 60) and $1,516 (+/- 45) in the group of children;
$1,245 (+/- 70) and $1,907 (+/- 48) in the group of adolescents; and
$1,402 (+/- 45) and $1,940 (+/- 31) in the group of adults.
The discounted total costs over the 3-year period were:
$2,166 (+/- 64) with usual care and $2,318 (+/- 43) with budesonide in the whole sample;
$2,581 (+/- 149) and $2,389 (+/- 108) in the group of children;
$1,855 (+/- 126) and $2,428 (+/- 91) in the group of adolescents; and
$2,056 (+/- 79) and $2,249 (+/- 47) in the group of adults.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER) was calculated to combine the costs and benefits of budesonide relative to usual care.
When the perspective of the health care system was adopted, the incremental cost per SFD gained was:

$11.3 (95% confidence interval, CI: 8.6 - 14.9) in the whole sample;

$10.5 (95% CI: 1.2 - 33.3) in the group of children;

$25.9 (95% CI: 14.2 - 66.4) in the group of adolescents; and

$9.4 (95% CI: 6.8 - 12.9) in the group of adults.

Under the societal perspective, the ICER was:

$3.7 (95% CI: 0.1 - 8) in the whole sample;

a negative figure (95% CI: -38.1 - 13.7), suggesting that budesonide dominated usual care, which was both more costly and less effective in the group of children;

$22.4 (95% CI: 8.4 - 64.3) in the group of adolescents; and

$3.4 (95% CI: 0.2 - 7.1) in the group of adults.

Variations in the discount rate had no impact on the results of the analysis. However, the unit costs of medications and daily wages were the variables with the greatest effect on the estimated ICERs.

Authors’ conclusions
The use of budesonide to treat patients with persistent asthma represented a cost-effective alternative to usual care in the USA. Better outcomes were achieved at a relatively small additional cost.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator (usual care) was appropriate. Usual care was not described but the authors stated that due to the pragmatic design of the study, patients in the control group were free to take their routine medications. You should decide whether this represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a well-designed clinical trial, which was appropriate for the study question. Power calculations were performed and double-blinding was used to avoid assessment bias. The study groups were comparable at baseline. The study sample was representative of the study population and sub-group analyses were conducted. The loss to follow-up was similar in both groups and the analysis of the clinical study was conducted on an intention to treat basis. These issues tend to enhance the internal validity of the analysis.

Validity of estimate of measure of benefit
The benefit measure was specific to the disease considered in the study. Hence, it may be difficult to compare it with the benefits of other health care interventions. However, the authors justified their choice of the SFDs as the summary benefit measure on the ground that this has been recognised as a clinical outcome with relevance to patients, providers and other decision-makers. Discounting was applied due to the long time horizon of the study.

Validity of estimate of costs
The authors adopted two distinct perspectives and it appears that all relevant categories of costs have been included in the analysis. Detailed information on the resources used, unit costs and price year were reported, thus permitting the replication of the study and reflation exercises in other settings. Discounting was relevant and was appropriately applied. Statistical tests were conducted and the cost estimates were selected in order to reflect US costs. The sources of
the data were provided. The results of the analysis were sensitive to the cost estimates used in the study.

**Other issues**
The authors compared their findings with those from other studies that showed similar results. However, the issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were conducted only on some cost items. The effectiveness results were more transferable since they came from a multi-centre trial. The study referred to patients with persistent asthma and this was reflected in the authors’ conclusions. Some limitations to the validity of the analyses were noted and discussed.

**Implications of the study**
The study results suggested that long-term budesonide treatment is cost-effective for patients with persistent asthma and is cost-saving in young patients.

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