Asthma: Resource use and costs for inhaled corticosteroid vs leukotriene modifier treatment—a meta-analysis

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Abstract

Objective To compare the effects of inhaled corticosteroid treatment with leukotriene modifier treatment on medical resource use and costs for asthma patients.

Study design Meta-analysis combining results from published and unpublished studies.

Data sources Studies were identified from the MEDLINE and EMBASE databases and the GlaxoSmithKline internal database study registers. Two independent reviewers evaluated the identified studies; studies meeting specified inclusion criteria were abstracted and summarized by meta-analysis with a random effects model.

Outcomes measured Hospitalization rate, emergency department visit rate, emergency department costs, drug costs, total asthma-related costs, and total medical care costs.

Results Patients taking inhaled corticosteroids had:

- a significantly lower annual rate of hospitalization than those taking leukotriene modifiers (2.2% vs 4.3%, respectively; $P<.05$)

- a greater decline in hospitalization rate (before vs after therapy initiation) than those taking leukotriene modifiers (decline of 2.4% vs 0.55%; $P<.01$)

- a lower annual rate of emergency department visits than those taking leukotriene modifiers (6.2% vs 7.7%; $P<.005$).

- lower total asthma-related medical costs than those taking leukotriene modifiers ($P<.05$) and a 17% reduction in overall total medical care costs (P not significant).

Conclusions Patients with asthma treated with inhaled corticosteroids had significantly fewer asthma-related hospitalizations and emergency department visits and lower total asthma-related health care costs than patients treated with leukotriene modifiers. These meta-analysis findings are consistent with results from randomized controlled trials showing improvements in lung function for patients taking inhaled corticosteroids as opposed to leukotriene modifiers.

Although many medications are available for patients with asthma, inhaled corticosteroids are generally the preferred treatment.[1–4] Multiple studies have demonstrated that inhaled corticosteroid therapy improves patient outcomes.[1] Inhaled corticosteroids have been shown to decrease costs[5] and use of medical care resources.[6–8]

More recently, leukotriene modifiers have been introduced for asthma treatment. This class of medication has bronchodilator and anti-inflammatory effects.[9] Although multiple studies have indicated improved outcomes and decreased costs associated with leukotriene modifier therapy in

certain patient populations,[10,11] its role in asthma management is uncertain.[9]

Several studies have compared the clinical outcomes of these therapies[12–15] and their impact on medical care resource use and costs.[16,17] However, these studies were not powered specifically to detect significant differences in resource use or costs.

We performed a meta-analysis to (1) compare the rate of hospitalization among patients with asthma treated with inhaled corticosteroids vs those treated with leukotriene modifiers and (2) evaluate other resource use rates and costs for these patients.

■ METHODS

The meta-analysis consisted of a literature search, the development of inclusion criteria, form development, and literature review.

Literature search

We searched the MEDLINE, EMBASE, Cochrane Collaboration Study Registry, and Glaxo-SmithKline databases and consulted experts in this field. The GlaxoSmithKline database consists of studies sponsored by GlaxoSmithKline that met companywide minimum quality thresholds and were published in full or abstract form.

We also contacted the manufacturers of leukotriene modifiers available in the United States, AstraZeneca and Merck, to request published and unpublished information on studies comparing leukotriene modifiers with inhaled corticosteroids. To provide results corresponding to current treatment patterns, only studies from 1991 to 2001 were included. Published and unpublished materials were included.[18,19]

Inclusion criteria

Studies were included in the meta-analysis if they met the following criteria.

Population. Patients with diagnosed asthma. Only studies that did not restrict analyses to severe asthma patients or children were included.

Study design. Prospective and retrospective

Hospitalization was significantly lower with inhaled corticosteroids than with leukotriene modifiers

comparative studies of patients receiving inhaled corticosteroid or leukotriene modifier monotherapy (no other controller therapy) in the same study. Studies were required to have defined inclusion and exclusion criteria, defined number of patients in each study arm, defined treatment protocol (ie, medications and doses used), and separate results for each medication.

Only studies presenting primary research (hence excluding review articles and meta-analyses) were included. Only studies presenting data for at least 6 months on all participants were included.

Outcomes. Hospitalization visit rates and costs, emergency department visit rates and costs, pharmacy costs, total asthma-related costs, and total medical care costs. Because resource use patterns and medical care cost information differs substantially between countries, we only included US studies.

Study process

Each identified article was evaluated by 2 independent reviewers (KMS and MG); any differences were discussed with a project leader to reach a consensus. Documents selected for inclusion were then reviewed by the 2 reviewers, and differences in data abstraction were resolved before inclusion.

Analysis

We used the Q statistic[20] to assess heterogeneity and, when appropriate, combined data from included studies with the use of a random effects model. Random effects methodology was used to assess the impact of inhaled corticosteroid vs leukotriene modifier therapy on the overall asthma population, not just the subpopulation of patients participating in included studies.[21]

Characteristics of studies included in the meta-analysis

Study	LOE*	Duration (mo)		Treatment (N)	Comparison (N)
		Before therapy	After therapy		
Oates and Gothard[22]	2b	9	9	Inhaled corticosteroids (546)[†]	Leukotriene modifiers (152)[‡]
Pathak et al[23]	2b	9	9	Fluticasone propionate (284)	Leukotriene modifiers (497)[‡]
Stanford et al[24]	1b	–	6	Fluticasone propionate (271)	Montelukast (262)
Stempel et al[16]	2b	9	12	Fluticasone propionate (602)	Zafirlukast (309)
Stempel et al[17]	2b	9	9	Fluticasone propionate (559)	Montelukast (382)
White et al[25]	2b	9	9	Inhaled corticosteroids (1305)[†]	Leukotriene modifiers (109)[‡]

*LOE, level of evidence. For an explanation of levels of evidence, see page 379.

[†]Results were presented for all inhaled corticosteroids combined.

[‡]Results were presented for all leukotriene modifiers combined.

Two sets of meta-analyses were performed with the abstracted data. First, the specified outcome measures were compared for patients taking inhaled corticosteroid vs leukotriene modifier therapy. Second, the impact (before vs after) of each treatment initiation was compared for each outcome.

Assessment of statistically significant differences between meta-analysis results was performed with the Student t test, with an α of .05. Charges were used in the included studies as proxies for costs. These costs were inflated to 2000 values by using the medical care component of the consumer price index before inclusion.

■ RESULTS

We identified 49 documents and reviewed them for inclusion in the meta-analysis; 6 (12.2%) met the inclusion criteria (**Table 1**). Five were retro-spective cohort studies; only 1 study was identified as a prospective trial comparing inhaled corticosteroid and leukotriene modifier therapies and including results on resource use or medical care costs.[16,17,22–25] All 6 studies were performed with support from GlaxoSmithKline.

Forty-three documents were excluded due to 1 or more of the following criteria: lack of primary results (9 documents, 21%); did not contain resource use rate or cost outcomes (22 documents, 51%); did not provide at least 6 months' worth of data on resource use or cost outcomes (5 documents, 12%); did not meet the defined inclusion and exclusion criteria (primarily studies not including both inhaled corticosteroid and leukotriene modifiers or those restricted to patient clinical subgroups; 10 documents, 34%); or did not define the number of patients included in the study (1 document, 3%).

TABLE 2

Meta-analysis results for inhaled corticosteroid vs leukotriene modifier therapy*

	Inhaled corticosteroids	Leukotriene modifiers	Inhaled corticosteroid vs leukotriene modifier patients[†]	
			Absolute difference	Relative difference
Annual asthma hospitalizations[‡]	2.23% (1.69–2.78)	4.30% (3.53–5.07)	−1.79% (−2.45 to −1.14)	−42.88% (−55.95 to −29.80)
Annual rate of visits to the emergency department due to asthma[§]	6.19% (4.84–7.53)	7.74% (6.30–9.19)	−1.53% (−1.78 to −1.28)	−21.35% (−25.31 to −17.38)
Total annual costs of visits to the emergency department	$93 (38–148)	$73 (52–94)	$21 (−17 to 59)	1.00% (−38 to 40)
Total annual drug costs[§]	$807 (548–1065)	$1062 (812–1312)	−$258 (−308 to −208)	−27.20% (−33.2 to −21.3)
Annual asthma-related cost[‡]	$882 (613–1150)	$1393 (1143–1643)	$513 (−392 to −634)	−38.01% (−47.4 to −28.8)
Total annual cost	$5254 (4474–6033)	$7140 (4970–9311)	−$1918 (−3509 to −327)	−17.20% (−30.9 to −3.5)

*Data are presented as mean (95% confidence interval).

[†]Absolute and relative differences were determined from meta-analyses of the absolute and relative differences for each included study.

[‡]Inhaled corticosteroid vs leukotriene modifier significant at P<.05.

[§]Inhaled corticosteroid vs leukotriene modifier significant at P<.005.

Because few studies presented data on the specified outcomes, we were unable to assess asthma-specific costs for subcategories of resource use. Too few studies included data on hospitalization costs (either asthma-specific or overall) to include in the analysis. Therefore, meta-analysis was performed on overall (ie, all causes) emergency department, pharmacy, and total medical care costs.

Primary analysis

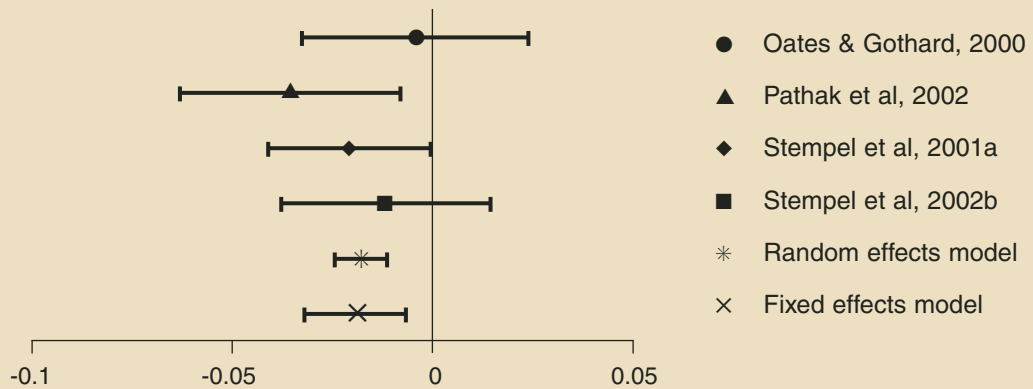The primary objective of this study was to evaluate the impact of inhaled corticosteroid and leukotriene modifier treatment on the mean annual hospitalization rate. Four of the 6 included studies contained information on hospitalization rate for each treatment. Results from the primary analysis are presented in **Table 2**.

Patients taking inhaled corticosteroids had a significantly lower annual rate of hospitalization than did patients taking leukotriene modifiers (2.23% vs 4.30%, respectively; P<.005). The absolute risk reduction was 2.07% (number needed to treat=48 for 1 year).

The difference in annual hospitalization visit rates for each study in the primary analysis is pre-

FIGURE

Difference in hospitalization rates (mean, confidence interval)

- ● Oates & Gothard, 2000
- ▲ Pathak et al, 2002
- ◆ Stempel et al, 2001a
- ■ Stempel et al, 2002b
- ✻ Random effects model
- ✕ Fixed effects model

-0.1   -0.05   0   0.05

Four included studies contained information on hospitalization rate for each treatment. The mean and 95% confidence interval for the difference are presented here; negative values reflect lower hospitalization rates among inhaled corticosteroid patients as compared with leukotriene modifier patients. Combining studies with the use of a random effects model (the default methodology for this article) or a fixed effects model produced similar results.

sented in the **Figure**, where negative values reflect lower hospitalization rates among patients taking inhaled corticosteroids than among those taking leukotriene modifiers. Two studies[16,23] had statistically significant differences in hospitalization rates, whereas the differences in the other 2 studies were not statistically significant (P<.05). Combining studies with the use of a random effects model (the default methodology for this analysis) or a fixed effects model produced similar results. The Q statistic indicated no significant heterogeneity (P=.43).

Secondary outcomes

Results of secondary analyses for 5 study outcomes (annual visits to the emergency department due to asthma, total emergency department costs, total drug costs, total asthma-related costs, and overall total cost) are presented in **Table 2**.

Mean annual rates of visits to the emergency department and total annual drug costs were significantly higher for patients taking leukotriene modifiers than for those taking inhaled corticosteroids (P<.005 for each). Patients taking

leukotriene modifiers had lower annual costs for visits to the emergency department than did those taking inhaled corticosteroids, although this difference was not statistically significant. The higher rate and lower cost of emergency department visits for patients taking leukotriene modifiers suggest that medical resources were used less at each visit as compared with those for patients taking inhaled corticosteroids.

Total asthma-related costs for patients taking inhaled corticosteroids were significantly lower than those for patients taking leukotriene modifiers (P<.05). Patients taking inhaled corticosteroids also incurred decreased annual total (all-cause) medical care costs. Although this difference was qualitatively large (approximately $1900, or a decrease of over 17%), it did not reach statistical significance.

Pre- vs post-initiation of therapy

In addition to comparing the impact of the 2 therapies on resource use and costs, we were interested in the impact of initiating each therapy on the study outcomes. We therefore assessed

TABLE 3

Resource utilization and costs before and after therapy initiation for inhaled corticosteroids vs leukotriene modifiers*

	Before vs after treatment, mean (95% confidence interval)		
	Inhaled corticosteroid patients	Leukotriene modifier patients	Absolute difference
Annual hospitalization rate	−2.37%[†] (−2.89 to −1.86)	−0.55% (−1.18 to 0.08)	−1.91%[‡] (−2.45 to −1.36)
Annual rate of visits to the emergency department due to asthma	−4.44%[§] (−5.98 to −2.90)	−2.06% (−3.61 to −0.51)	−2.47%[||] (−3.09 to −1.86)
Total annual costs of the emergency department	−$5 (−21 to 10)	−$15 (−44 to 15)	$9 (−33 to 51)
Total annual drug costs	$415[†] (312–517)	$579[†] (472-686)	−$167[||] (−192 to 142)
Total annual medical care costs	$641[†] (113–1169)	$1712[†] (927–3529)	−$1080 (−2802 to 643)

*Post-therapy initiation values for inhaled corticosteroids and leukotriene modifiers are presented in Table 1.

[†]Before vs after treatment initiation significant at *P*<.005.

[‡]Before vs after treatment initiation outcomes for inhaled corticosteroids vs leukotriene modifiers significant at *P*<.01.

[§]Before vs after treatment initiation significant at *P*<.05.

[||]Before vs after treatment initiation outcomes for inhaled corticosteroids vs leukotriene modifiers significant at *P*<.001.

resource use rates and costs before and after treatment initiation. These patients may have been receiving asthma therapies (or no asthma therapy) other than inhaled corticosteroids or leukotriene modifiers. The number of studies presenting data on costs was too small to allow comparison.

Results of this within-group analysis are presented in **Table 3**. For patients taking inhaled corticosteroids, hospitalization rates and emergency department visit rates decreased significantly after treatment initiation compared with the pre-initiation values (*P*<.005 and *P*<.05, respectively). The decreases for patients taking leukotriene modifiers upon treatment initiation were smaller and not statistically significant.

Both groups showed similar small decreases in annual emergency department costs, neither of which was significant. The increases in annual total drug costs and annual total medical care costs after treatment initiation were significant for both groups of patients (all at *P*<.005). However, both increases were greater for patients taking leukotriene modifiers; the increase in drug costs was statistically significant (*P*<.001).

■ DISCUSSION

In this study, we used meta-analysis to combine data across studies and determine more robust estimates of the impact of inhaled corticosteroid vs leukotriene modifier therapy on medical resource use rates and costs. The primary analysis indicated that annual hospitalization rates among patients taking inhaled corticosteroids

> Increases in medical care costs after treatment initiation were significant for those on both medications

are significantly lower that those taking leukotriene modifiers. Other resource use rates and costs evaluated in this study also generally showed decreased values for patients taking inhaled corticosteroids.

Although meta-analysis generally has been used for clinical outcome measures, it is a highly appropriate method for resource use and cost outcomes. In general, studies of the impact of a particular treatment are powered to assess safety and efficacy or effectiveness; there is often insufficient power to detect differences in resource use or costs in any one study. Due to substantial variation in treatment patterns, the variance associated with resource use rates (and associated costs) may be substantially higher than that for clinical measures; such a wide variance adds to the difficulties in assessing differences for nonclinical outcomes.

Limitations

This study has a number of limitations. Only a few studies met inclusion criteria for the meta-analysis; the analysis should be replicated as additional studies become available. Data were abstracted from the included studies without modification (except for inflating costs to 2000 values when necessary). As in all meta-analyses, any problems present in the original data are present in the combined data; limitations of the original data are not addressed by this method.

Among the studies evaluated for the meta-analysis were a number published only as abstracts. Inclusion of unpublished literature in meta-analyses is controversial; however, several sources[18,19] now recommend inclusion of published and unpublished studies. Egger and Smith[26] found that studies with significant results are more likely to be published than are studies with nonsignificant results, leading to publication

bias. Studies with significant results also may be more likely to be published in indexed journals, leading to "database bias." As such, inclusion of unpublished studies is important to produce unbiased results.

Five of the 6 studies that met the inclusion criteria were observational, retrospective cohort analyses. Whereas many meta-analyses focus solely on prospective, randomized clinical trials, several have included retrospective data.[27,28] Retrospective analyses and observational data have a number of limitations, in particular the lack of randomization that can lead to differences in characteristics of specified treatment groups. Further, as discussed by Egger et al,[29] meta-analyses based on observational studies may involve bias and confounding.

However, observational data and retrospective analyses also have the advantage of reflecting "real world" treatment patterns and broader patient groups that increase the generalizability of the data, whereas clinical trials may include protocol-driven utilization and selected patient groups. Clinical trials also may occur in specialized health care settings, whereas observational (cohort) data may be more applicable to clinical practice. Due to these factors, meta-analysis of observational data has become common.[29]

The pre-initiation vs post-initiation analysis indicated that values for each treatment group provide information on the similarities between treatment groups before initiation of controller therapy. Even though the treatment groups were not randomized to each therapy and we have no means to ensure compatibility between groups, having similar rates of resource use between groups provides some evidence regarding similarity. Nonetheless, given the limitations of the retrospective data and meta-analysis in general, it will be important to validate the results of this meta-analysis in the future with naturalistic prospective studies.

Despite these limitations, this study provides important information on the impact of asthma therapies on resource use and costs. Specifically,

the resource use and cost outcomes assessed in this study were lower for inhaled corticosteroid patients than for leukotriene modifier patients. This study also illustrates the usefulness of meta-analysis in evaluating resource use and costs. By selecting and combining outcomes across studies in a standardized, rigorous, and transparent manner, the effects of different therapies can be evaluated with greater precision.

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