

Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of current evidence

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Abstract

Objective To compare the safety and efficacy of anti-leukotrienes and inhaled glucocorticoids as monotherapy in people with asthma.

Design Systematic review of randomised controlled trials comparing anti-leukotrienes with inhaled glucocorticoids for 28 days or more in children and adults.

Main outcome measure Rate of exacerbations that required treatment with systemic glucocorticoids.

Results 13 trials (12 in adults, one in children) met the inclusion criteria; all were in people with mild and moderate asthma. Leukotriene receptor antagonists were compared with inhaled glucocorticoids at a daily dose equivalent to 400-450 µg beclometasone dipropionate. Patients treated with leukotriene receptor antagonists were 60% more likely to suffer an exacerbation requiring systemic glucocorticoids (relative risk 1.6, 95% confidence interval 1.2 to 2.2; number needed to treat 27, 13 to 81). A 130 ml greater improvement (80 ml to 170 ml) in forced expiratory volume in one second and a 19 l/min greater increase (14 l to 24 l) in morning peak expiratory flow rate were noted in favour of inhaled glucocorticoids. Differences in favour of inhaled glucocorticoids were also observed for nocturnal awakenings, use of rescue β_2 agonists, and days without symptoms. Risk of side effects was no different between groups, but leukotriene receptor antagonists were associated a 2.5-fold increase risk of withdrawals due to poor asthma control (relative risk 2.5, 1.8 to 3.5).

Conclusions Inhaled glucocorticoids doses equivalent to 400 µg/day beclometasone are more effective than leukotriene receptor antagonists in the treatment of adults with mild or moderate asthma. There is insufficient evidence to conclude on the efficacy of anti-leukotrienes in children.

Introduction

Anti-leukotrienes are a new class of anti-inflammatory drugs that interfere directly with leukotriene production or leukotriene receptors.¹ They are administered orally and seem to lack the adverse effects associated with long term systemic glucocorticoid therapy.

The 2002 Global Initiative for Asthma guidelines classify the role of anti-leukotrienes as still under investigation,² although several national guidelines advocate their use as adjunct therapy to inhaled glucocorticoids for moderate to severe persistent asthma or as alternative single agent management in those with mild asthma.³⁻⁵ In 2001, their sales in the United States almost equalled those of inhaled glucocorticoids, representing nearly 30% of the market share for antiasthmatic drugs, while they accounted for less than 10% of the market share in Canada and the United Kingdom (D Rhodes, IMS Health, personal communication, 2002). This variability among countries attests to the confusion related to their relative efficacy and safety. In 2000 a systematic review of 10 randomised controlled trials, with complete data for only two trials, tentatively concluded that asthma control was better with inhaled glucocorticoids as single agents than with anti-leukotrienes.⁶ With the recent publication of several trials, it seems timely to update this Cochrane review.

Methods

Identification of trials—I searched Medline, Embase, CINAHL, and central (Cochrane controlled trials register) databases in January 2002, checked bibliographies of identified trials and review articles and contacted the international headquarters of pharmaceutical companies that produce anti-leukotrienes and inhaled glucocorticoids.

Study selection—Trials included were all randomised controlled trials that compared anti-leukotrienes with a stable dose of inhaled glucocorticoid for at least 28 days in adults and children aged 2 years and above. No additional antiasthmatic drugs were allowed, other than rescue short acting β_2 agonists and systemic glucocorticoids. There was no restriction on language.

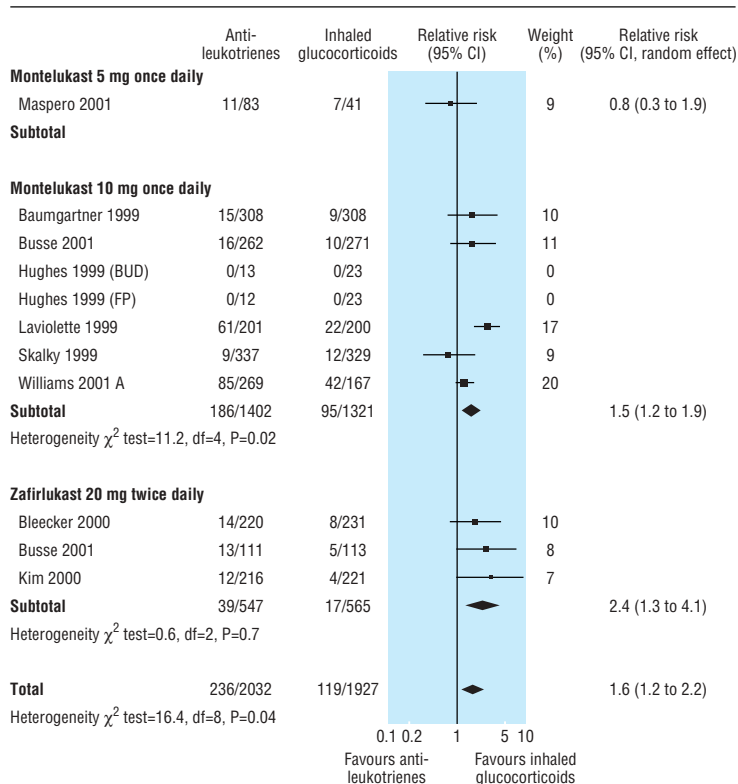
Data collection—Two independent reviewers considered each potentially relevant trial for inclusion, assessed study quality, and extracted data. Disagreements were resolved by consensus. Authors or sponsors of each included trial were contacted to verify the accuracy of the methodology and extracted data.

Statistics—The a priori specified primary outcome was the number of exacerbations requiring systemic glucocorticoids. Secondary outcomes included lung function, nocturnal awakenings, use of rescue β_2 agonist,

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BMJ 2003;326:621-3



Pooled relative risk of patients experiencing at least one exacerbation requiring systemic glucocorticoids (one count per patient) comparing leukotriene receptor antagonists with inhaled glucocorticoids. Trials stratified according to dose and leukotriene receptor antagonists used. Hughes' trial tested two inhaled glucocorticoid preparations: 400 µg budesonide (BUD) and 200 µg fluticasone propionate (FP) against montelukast. To prevent over-representation of anti-leukotriene group, sample size of 25 of montelukast group was reduced by half for analysis. χ^2 test for heterogeneity was considered significant if $P < 0.10$

adverse effects, and withdrawal rates. Equivalence was assumed if the summary estimate of relative risk and its 95% confidence limits were within 10% of the line indicating no difference. Homogeneity of effect sizes among pooled studies was tested for and heterogeneity was explored using a priori subgroup analyses of the anti-leukotriene tested; the dose and inhaled glucocorticoid used; severity of asthma (mild, moderate); and patient age (child, adult). Sensitivity analyses were conducted to investigate the effect on study results of quality of methods, publication bias, and funding bias, and funnel plot analysis was carried out to look for publication bias. The fail safe N test (the number of non-included trials with null results needed to negate current findings) assessed the robustness of the results. See bmj.com for details of statistical analysis.

Results

Description of studies

The search strategy yielded 451 citations. Thirteen trials met the inclusion criteria, of which five were new trials not included in the previous review (see bmj.com for full list of references). Two trials included in the previous analysis failed to meet the inclusion criteria based on new information and four trials were available in abstract form only.

All trials had a parallel group design and 10 were of high methodological quality. Confirmation of methods and data extraction was obtained from the authors of

12 trials, including voluntary disclosure of data for the four unpublished studies. Double blinding was reported by all but three trials, which used an open label design. Most trials reported appropriate randomisation methods; two trials reported insufficient details or inappropriate randomisation.

The studies were relatively homogeneous in the age and sex of participants, daily dose of inhaled glucocorticoids tested (that is, equivalent to 400 µg chlorofluorocarbon (CFC) propelled beclometasone), and intention to treat analysis. Only one trial dealt with children. Four trials focused on people with mild asthma, eight trials with moderate asthma, and one trial failed to report asthma severity.

Exacerbations requiring systemic glucocorticoids

Patients treated with leukotriene receptor antagonists were 60% more likely to experience an exacerbation requiring systemic glucocorticoids than those treated with inhaled glucocorticoids (11 trials; relative risk 1.6, 95% confidence interval 1.2 to 2.2; (figure). Twenty seven people (13 to 81) would need to be treated with inhaled glucocorticoids instead of leukotriene receptor antagonists to prevent an exacerbation requiring systemic glucocorticoids. The funnel plots indicated no evidence of systematic bias. The fail safe N was 59 trials—that is, 59 additional trials with null results would be needed to reverse the findings.

Source of heterogeneity

No a priori factor was a major determinant of the magnitude of effect. The leukotriene receptor antagonist (χ^2 test=1.86, df=1, $P > 0.10$), the inhaled glucocorticoid preparation used (1.86, df=1, $P > 0.10$), and the baseline severity (2.52, df=1, $P > 0.10$) failed to explain the difference among studies in the magnitude of effect. There was no group difference in the only paediatric trial (relative risk 0.78, 0.32 to 1.85). Because all trials contributing data to this outcome used doses equivalent to 400 µg/day CFC beclometasone, the strength of the inhaled glucocorticoids could not explain the observed heterogeneity. Sensitivity analyses did not show any significant influences of quality of methods, intention to treat analysis, publication status, or funding source.

Secondary outcomes

There were significant group differences in favour of inhaled glucocorticoids for the several outcomes at all points in time. Within six weeks of treatment, compared with patients in the anti-leukotriene group, patients treated with inhaled glucocorticoids experienced a significantly greater improvement from baseline in forced expiratory flow in one second (eight trials; weighted mean difference 130 ml, 80 ml to 170 ml) and morning peak expiratory flow (seven trials; 19 l/min; 14 l to 25 l); fewer nocturnal awakenings a week (five trials; -0.56, -0.28 to -0.77); less rescue use of β_2 agonists (six trials; -0.78, -0.55 to -1.00 puffs a day); and fewer days with symptoms (three trials; -9%, -5% to -13%).

Anti-leukotriene treatment was associated with an increased risk of withdrawal because of poor asthma control (12 trials; relative risk 2.5, 1.8 to 3.5). There was no group difference in the number of patients who experienced "any adverse effects" (11 trials; 1.0, 0.9 to 1.1). There were no differences between the groups in increase in liver enzyme activity, headache, oral candidiasis, nausea, and death.

Discussion

In adults with mild to moderate chronic asthma the risk of exacerbations requiring systemic glucocorticoids was 60% higher with daily oral leukotriene receptor antagonists than with doses of inhaled glucocorticoid equivalent to 400 µg/day inhaled beclometasone. The effect was not influenced by the anti-leukotriene or inhaled corticosteroid used, disease severity, quality of methods, intention to treat analysis, publication status, or funding source. The 24 week trial in children with mild asthma showed no group difference, but the results failed to meet the a priori definition of equivalence. The small number of trials precluded the use of meta-regression analysis so the individual effect of these factors could not be identified.⁷

Inhaled glucocorticoids at doses equivalent to 400 µg/day beclometasone dipropionate were more effective than leukotriene receptor antagonists in improving spirometry; increasing the percentage of days without symptoms; and reducing night awakenings and rescue use of β₂ agonists. The higher rate of withdrawals in the anti-leukotriene group because of poor asthma control supported the above findings. Results were relatively similar among trials regardless of the leukotriene receptor antagonist and inhaled steroid used. When heterogeneity was identified, the anti-leukotriene used failed to explain the variation among trial results. The superiority of inhaled glucocorticoids was evident within four to six weeks and persisted for up to 37 weeks. The exact glucocorticoids dose equivalence of leukotriene receptor antagonists remains to be determined.

The risk of overall adverse effects was similar in both groups, meeting our a priori definition of equivalence. No rare adverse effects were reported. Adverse effects typically associated with inhaled glucocorticoids were not measured, preventing a fair comparison of the safety profile on long term use.

This review completes the assessment of the role of anti-leukotrienes in the treatment of asthma, together with the recent review on their use as additional treatment to inhaled glucocorticoids.⁸ The identification of unpublished trials from producers of anti-leukotrienes and inhaled glucocorticoids argues against important selection bias. With only one paediatric trial, however, the results should be generalised to children with caution.

I acknowledge the collaboration of Christopher Miller and Susan Shaffer (AstraZeneca, USA), Theodore F Reiss and G P

What is already known on this topic

In 2000 a Cochrane systematic review tentatively concluded that control of asthma was better in patients treated with inhaled glucocorticoids as single agents than with anti-leukotrienes

The 2002 Global Initiative for Asthma guidelines still classify the role of anti-leukotrienes as "under investigation"

What this study adds

Anti-leukotrienes as single agent are less effective than low doses of inhaled glucocorticoids for patients with mild and moderate persistent asthma

Noonan (Merck Frosst, USA), and Shailesh Patel and Rob Pearson (GlaxoSmithKline, UK), who confirmed the methods and data extraction and voluntarily disclosed additional data. I thank Giselle Hicks for her participation in the identification of eligible trials, assessment of methods and data extraction, and data entry. I am indebted to the Cochrane Airways Review Group—namely, Toby Lasserson and Karen Blackhall, for the literature search and ongoing support, and Paul Jones and Christopher Cates, for their constructive comments.

Contributors: See bmj.com

Funding: Senior salary award of the Fonds de la Recherche en Santé du Québec. No research funding was available for the review. The guarantor accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

Competing interests: The author has received travel support, research funds, and fees for speaking from AstraZeneca, producer of zafirlukast; Merck Frosst, producer of montelukast; and Glaxo-SmithKline, producer of inhaled glucocorticoid preparations with which leukotriene receptor antagonists were compared.

- 1 Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *New Engl J Med* 1999;340:197-206.
- 2 Global Initiative for Asthma. *Global strategy for asthma management and prevention*. Bethesda, MD: National Heart, Lung and Blood Institute, 2002 (NIH Publication 02-3659). www.ginasthma.com/
- 3 National Asthma Education and Prevention Program. *NAEPP expert panel report guidelines for the diagnosis and management of asthma*. 2002; Bethesda, MD: National Heart, Lung and Blood Institute, 2002 (NIH Publication 02-5075). www.nhlbi.nih.gov/guidelines/asthma/index.htm
- 4 Boulet LP, Bai TR, Becker A, Berube D, Beveridge R, Bowie DM, et al. What is new since the last (1999) Canadian Asthma Consensus Guidelines? *Can Respir J* 2001;8(suppl A):5-27a.
- 5 The British guidelines on asthma management. *Thorax* 1997;52(suppl):S1-21.
- 6 Ducharme FM, Hicks G. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma. *Cochrane Database Syst Rev* 2000;(3):CD002314.
- 7 Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693-708.
- 8 Ducharme FM. Anti-leukotrienes as add-on therapy to inhaled glucocorticoids in patients with asthma: systematic review of current evidence. *BMJ* 2002;324:1545-52.

(Accepted 29 January 2003)

One hundred years ago

The German Emperor and the medical profession

The Emperor William has lately, it is said, delivered himself of an opinion that there are too many lawyers in Germany, and declared that more young men should study medicine. The Imperial utterances are always interesting even when they are not particularly illuminating, but the interest in this case is, we fear, of a somewhat melancholy character as far as our brethren of the Fatherland are concerned. They are already complaining bitterly of the overcrowding of the profession. There are now 28,174 medical practitioners in the German Empire, and during the last five years the number of doctors has increased by 18.6 per cent., while the general population has increased by 7.8 per cent. The

professional struggle for life is no where more severe than in Germany, and, in addition to the stress of competition caused by numbers, practitioners have to fight for a pittance against quacks who to a large extent are not interfered with, and in some parts of the Empire are actually protected by the law. That the Emperor should wish for fewer lawyers is intelligible enough; but why he should wish for more doctors is a mystery which we cannot pretend to fathom. Would it be *lèse majesté* to suggest that His Imperial Majesty spoke in his haste without thinking, or without knowing the conditions of life among an important section of his own subjects?
(*BMJ* 1903;ii:1332)