

Anti-leukotrienes as add-on therapy to inhaled glucocorticoids in patients with asthma: systematic review of current evidence

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Abstract

Objectives To examine the evidence for the efficacy and glucocorticoid sparing effect of oral anti-leukotrienes taken daily as add-on therapy to inhaled glucocorticoids in patients with asthma.

Design Systematic review of randomised controlled trials of children and adults with asthma comparing the addition of anti-leukotrienes or placebo to inhaled glucocorticoids.

Main outcome measures The rate of exacerbations of asthma requiring rescue systemic glucocorticoids when the intervention was compared to the same or double dose of inhaled glucocorticoids, and the glucocorticoid sparing effect when the intervention was aimed at tapering the glucocorticoid.

Results Of 376 citations, 13 were included: 12 in adult patients and one in children. The addition of licensed doses of anti-leukotrienes to inhaled glucocorticoids resulted in a non-significant reduction in the risk of exacerbations requiring systemic steroids (two trials; relative risk 0.61, 95% confidence interval 0.36 to 1.05). No trials comparing the use of anti-leukotrienes with double the dose of inhaled glucocorticoids could be pooled. The use of anti-leukotrienes resulted in no overall group difference in the lowest achieved dose of inhaled glucocorticoids (three trials; weighted mean difference $-44.43 \mu\text{g}/\text{day}$, -147.87 to 59.02 ; random effect model) but was associated with a reduction in withdrawals owing to poor asthma control (four trials; relative risk 0.56, 0.35 to 0.89).

Conclusions The addition of anti-leukotrienes to inhaled glucocorticoids may modestly improve asthma control compared with inhaled glucocorticoids alone but this strategy cannot be recommended as a substitute for increasing the dose of inhaled glucocorticoids. The addition of anti-leukotrienes is possibly associated with superior asthma control after tapering of glucocorticoids, but the glucocorticoid sparing effect cannot be quantified at present.

Introduction

Inhaled glucocorticoids are the cornerstone of asthma management.¹ When the control of asthma is poor, other drugs such as long acting β_2 agonists and

anti-leukotrienes can be added.²⁻⁴ Anti-leukotrienes are a new class of anti-inflammatory drugs.⁵ Thus the combination of anti-leukotrienes and inhaled glucocorticoids may enhance the control of asthma by reducing bronchoconstriction and inflammation of the airways.

We examined the safety and efficacy of oral anti-leukotrienes as add-on therapy to inhaled glucocorticoids in children and adults with asthma to quantify the improvement in asthma control achieved over inhaled steroids alone (at the same or double the dose) and the glucocorticoid sparing effect when inhaled steroids are tapered.

Methods

Identification of trials

We searched Medline, Embase, Cinahl, and Central (Cochrane controlled trials register) databases up to August 2001; for the detailed search strategy see *bmj.com*. We checked the references of all identified trials and review articles, and we searched the abstract books of the international meeting of the American Thoracic Society for 1998, 1999, and 2000. We contacted the international headquarters of pharmaceutical companies producing anti-leukotrienes to obtain or to identify unpublished trials.

Study selection

We included trials if they met the following criteria: they were randomised controlled trials, they pertained to children and adults with asthma who were taking inhaled glucocorticoids for maintenance, they compared the addition of anti-leukotrienes or placebo daily to inhaled glucocorticoids for a minimum of 28 days. The primary outcome measures were the number of exacerbations of asthma requiring rescue systemic glucocorticoids when the intervention was compared with the same or an increased dose of inhaled glucocorticoids and the change from the baseline dose of inhaled glucocorticoids required to maintain control when the intervention was aimed to establish the steroid sparing effect. Secondary outcomes were changes in pulmonary function tests, symptoms, use of rescue β_2 agonists, quality of life, exacerbations requiring hospital admission, adverse effects, and withdrawals. The quality of the methods of each trial was assessed with the Jadad's instrument.⁶

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Table 1 Characteristics of included trials

Trials	No of patients	Publication status	Industry sponsored trials	Mean age (years)	% male	Baseline FEV ₁ (mean % predicted)	Atopy	Dose optimisation before randomisation	Drug (dose) of anti-leukotrienes‡	Inhaled glucocorticoids			Duration of treatment (weeks)	Intention to treat analyses	Reported outcomes	
										Drug	Intervention group	Control group			Exacerbations requiring systemic steroids	Steroid dose reduction
Anti-leukotrienes versus placebo as add-on therapy to inhaled glucocorticoids																
Lavolette et al ⁷	393	Yes	Merck	40	54	72	75		Montelukast (10 mg once daily)	Beclomethasone dipropionate	400 µg	400 µg	16	Yes	No	
Simons et al ^{8†}	279	Yes	Merck	10	67	78	72		Montelukast (5 mg once daily)	Budesonide	400 µg	400 µg	4	Yes	Yes	
Tamaoki et al ⁹	79	Yes	No	48	43	80*	Not reported		Pranlukast (450 mg twice daily)	Beclomethasone dipropionate	750 µg	750 µg	6	Not reported	Yes	
Tomita et al ¹⁰	41	Yes	Not reported	50	60	88*	66		Pranlukast (450 mg once daily)	Beclomethasone dipropionate	400 µg	400 µg	8	Not reported	No	
Virchow et al ¹¹	368	Yes	Astra-Zeneca	48	51	64	46		Zafirlukast (80 mg twice daily)	Beclomethasone dipropionate	1598 ± 381 µg	1650 ± 456 µg	6	Yes	Yes	
Wada et al ¹²	80	Yes	No	50	50	74	53		Pranlukast (225 mg twice daily)	Beclomethasone dipropionate	1048 ± 237 µg	1127 ± 307 µg	4	Not reported	No	
Anti-leukotrienes as add-on therapy to inhaled glucocorticoids versus double dose of inhaled glucocorticoids																
Nayak et al ¹³	394	No	Astra-Zeneca	39	38	67	94		Zafirlukast (40 mg or 80 mg twice daily)	Beclomethasone dipropionate	400 µg	800 µg	13	No	Yes	
Ringdal et al ¹⁴	440	No	Astra-Zeneca	41	49	85	Not reported		Zafirlukast (20 mg or 80 mg twice daily)	Beclomethasone dipropionate	400-500 µg	800-1000 µg	12	No	Yes	
Anti-leukotrienes versus placebo as add-on therapy to tapering doses of inhaled glucocorticoids																
Baba et al ¹⁵	24	No	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Pranlukast (not reported)	Beclomethasone dipropionate	Not reported	Not reported	Not reported	Not reported	No	No
Bateman et al ¹⁶	359	No	Astra Zeneca	42	45	2.6L	48	0	Zafirlukast (20 mg twice daily)	Beclomethasone dipropionate or Budesonide	400-750 µg	400-750 µg	20	Yes	No	Yes
Laitinen et al ¹⁷	262	No	Astra Zeneca	44	42	2.5L	43	2 weeks to 3 months	Zafirlukast (20 mg twice daily)	Beclomethasone dipropionate or Budesonide	800-2000 µg	800-2000 µg	12	No	No	Yes
Lotdahl et al ¹⁸	226	Yes	Merck	40	43	83	Not reported	≤7 weeks	Montelukast (10 mg once daily)	Various‡	300-3000 µg	300-3000 µg	12	Yes	No	Yes
Shingo et al ¹⁹	22	No	Merck	39	41	84	Not reported	0	Montelukast (10 mg once daily)	Various§	1600 µg	1350 µg	8	Yes	Yes	No

FEV₁=forced expiratory volume in one second. Anti-leukotriene licensed doses for adults: Montelukast: 10 mg once daily (5 mg for children aged 5 to 14 years), Pranlukast 225 mg twice daily, Zafirlukast 20 mg twice daily. No trial reported use of inhaled glucocorticoids propelled by hydrofluorocarbons.*Reported spirometry before abrupt reduction by half of maintenance dose of inhaled glucocorticoids.†Cross over study. ‡Reported use of beclomethasone dipropionate (16%), budesonide (22%), flunisolide(15%), fluticasone propionate (7%), and triamcinolone acetonide (40%). Corticosteroids dose reduction not been in µg of "chlorofluorocarbon propelled beclomethasone dipropionate equivalent" (T R Reiss, personal communication, 2000). §Reported use of triamcinolone acetonide (72%), flunisolide (18%), and beclomethasone dipropionate (9%).

Results

Of the 376 identified citations, we included 13 trials (six unpublished) in the review (table 1). The quality of methods of 10 trials was rated high (≥4) and was confirmed by authors in all cases; in the remaining three trials allocation was not concealed.^{10 12 15}

Anti-leukotrienes versus placebo as add-on therapy to inhaled glucocorticoids

Although four^{7-9 11} of the six^{10 12} identified trials contributed data to the primary outcome, only two tested anti-leukotrienes (montelukast; Singular, Merck Frosst) at licensed doses.^{7 8} With the addition of licensed doses of anti-leukotrienes to glucocorticoids, a non-significant reduction in the risk of exacerbations requiring systemic steroids was observed (relative risk 0.61, 95% confidence interval 0.36 to 1.05). The only paediatric trial did not show any significant group difference. When higher doses were examined, the addition of pranlukast (Ono, Japan) or zafirlukast (Accolate, Astra Zeneca) reduced the risk of exacerbations requiring systemic steroids by 66% (relative risk 0.34, 0.13 to 0.88) (fig 1). The number needed to treat was 20 (11 to 100).

Pooling of the two trials testing the use of licensed doses of montelukast for four or 16 weeks showed significant but modest group differences in favour of anti-leukotrienes in the change from baseline in morning peak expiratory flow rate (weighted mean difference 7.71 l/min, 2.98 to 12.44), use of β₂ agonists (-0.32 puffs/day, -0.56 to -0.08), and eosinophil counts (-0.07 × 10⁹/l, -0.14 to 0.00).^{7 8} No significant group difference was observed in the change in forced expiratory volume in one second (0.07 litres, -0.01 to 0.16) or in the risk of overall withdrawals (relative risk

0.91, 0.54 to 1.53), withdrawals owing to adverse effects (0.65, 0.26 to 1.66), increased concentrations of liver enzymes (1.02, 0.36 to 2.88), headache (1.16, 0.86 to 1.57), and nausea (0.45, 0.19 to 1.07).

Pooling of the two trials of higher than licensed doses of pranlukast or zafirlukast for six weeks showed a significant group difference favouring the addition of anti-leukotrienes to inhaled corticosteroids. This was shown in the magnitude of improvement from baseline in forced expiratory volume in one second (weighted mean difference 0.10 litres; 0.01 to 0.20), peak expiratory flow (27.2 l/min, 18.6 to 35.8), use of rescue β₂ agonists (-0.43, -0.22 to -0.63), and asthma symptoms (standardised mean difference -0.46, -0.25 to -0.66).^{9 11} No group difference in overall adverse events or nausea was observed; insufficient number of trials prevented pooling of data for other adverse effects.

Anti-leukotrienes as add-on therapy to inhaled glucocorticoids versus double dose inhaled glucocorticoids

The data from two unpublished trials, each testing two different doses of zafirlukast, were analysed.^{13 14} Pooling of data was only possible for zafirlukast at four times the licensed dose. No apparent group difference was found in the risk of an exacerbation requiring systemic steroids after 12 weeks of treatment with zafirlukast 80 mg twice daily (relative risk 1.08, 0.47 to 2.50).

No group difference was found in secondary outcomes. Zafirlukast (80 mg twice daily) was associated with an increased risk of increased concentrations of liver enzymes (1 in every 25 patients, 95% confidence interval 14 to 100) and 1 in every 33 (16 to ∞) patients would withdraw due to adverse events. In

contrast, a double dose of beclomethasone was associated with a higher risk of oral moniliasis compared with anti-leukotrienes (number needed to harm 33, 17 to 100).

Anti-leukotrienes versus placebo as add-on therapy to tapered doses of inhaled glucocorticoids

After 12 weeks of treatment, two trials of zafirlukast reported no significant group difference in final mean symptom scores and use of β_2 agonists.^{16 17} Trends approaching significance favouring the intervention were observed in the final forced expiratory volume in one second (weighted mean difference 0.12 litres, -0.02 to 0.27) and final peak expiratory flow (14.47 l/min, -4.54 to 33.48). Two trials testing montelukast failed to report sufficient data to confirm comparable asthma control after steroid tapering.^{18 19} Pooling of the four trials showed a noticeable reduction (relative risk 0.56, 0.35 to 0.89) in the rate of withdrawal owing to poor asthma control in the group treated with anti-leukotrienes, suggesting better asthma control with the combination therapy.

After 12 to 20 weeks of treatment, no overall group difference was observed in change from the baseline dose of inhaled glucocorticoid required to maintain asthma control (three trials; weighted mean difference 1.87%, -3.52% to 7.27%). When the lowest tolerated dose of inhaled glucocorticoids was considered, no meaningful group difference was observed either (-44 $\mu\text{g}/\text{day}$, -148 to 59) (fig 2). Based on the relative potency and distribution of inhaled steroids used in the montelukast trial (table 1), the 200 $\mu\text{g}/\text{day}$ would translate to an approximate corticosteroid sparing effect of 160 $\mu\text{g}/\text{day}$ of beclomethasone equivalent.³ The rate of complete glucocorticoid weaning was similar between groups (three trials, relative risk 1.18, 0.95 to 1.47).

No group difference was found in the number of overall withdrawals, withdrawals owing to adverse effects (relative risk 1.07, 0.57 to 2.03), increased concentrations of liver enzymes (2.13, 0.80 to 5.68), headache (0.90, 0.64 to 1.26), or nausea (1.14, 0.49 to 2.67). The similarity between groups in the number of overall adverse effects met our definition of equivalence (0.98, 0.91 to 1.05). A significantly increased risk of serious adverse events as defined by the criteria of the Federal Drug Administration was associated with zafirlukast at licensed doses (2.47, 1.53 to 3.97).^{16 17 20}

Discussion

Strengths and limitations of the review

This meta-analysis is limited by the quantity and quality of existing data. Despite the abundance of literature on anti-leukotrienes, only 8% of randomised controlled trials were designed to assess the role of anti-leukotrienes as add-on therapy to inhaled glucocorticoids; most of the excluded trials compared anti-leukotrienes with placebo in groups of patients comprised of, or including, those naïve to steroids. Publication bias was evident: of the five trials involved in the glucocorticoid tapering protocol, only the one in favour of anti-leukotrienes is published.⁶ A thorough systematic search resulted in the identification of unpublished trials of high quality methods, increasing the power and scope of the review.²¹ The value of this

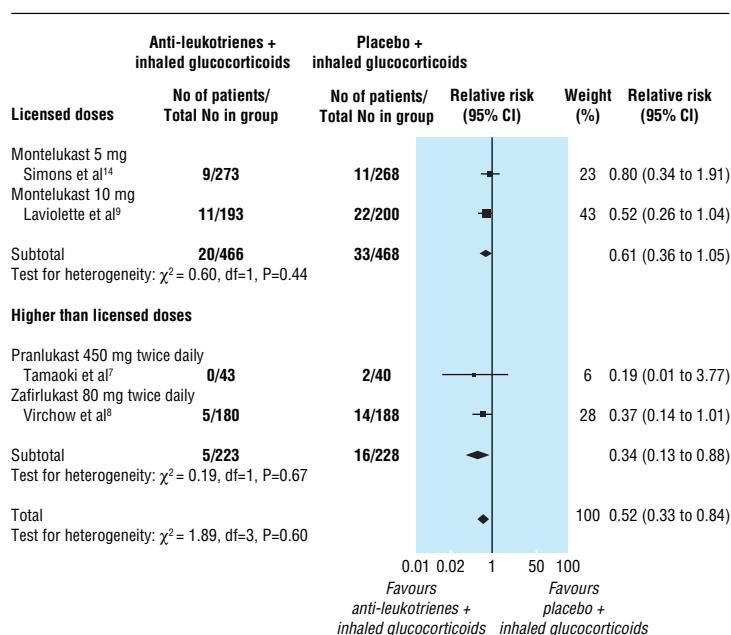


Fig 1 Anti-leukotrienes versus placebo as add-on therapy to inhaled glucocorticoids

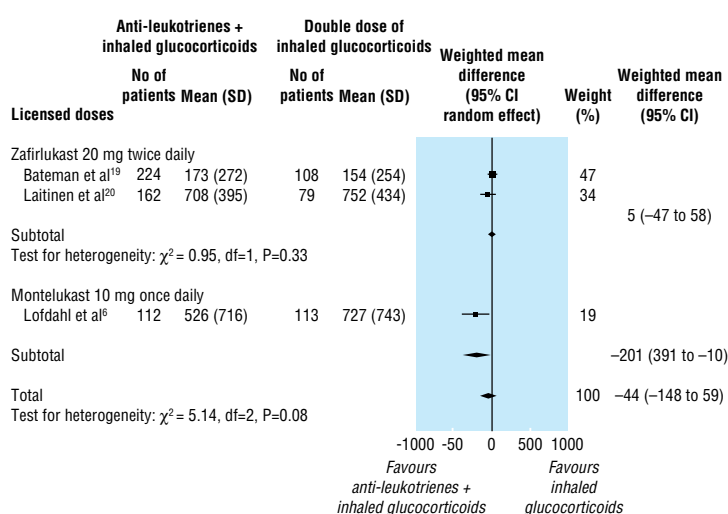


Fig 2 Anti-leukotrienes versus placebo with tapering doses of inhaled glucocorticoids

review is strengthened by the direct confirmation of methods and extracted data from the authors or sponsors of nine of the 13 trials and the voluntary disclosure of data for five unpublished trials.^{13 14 16 17 19} Because the number and size of studies pooled under each protocol were small, the robustness of analyses of different inhaled glucocorticoids and anti-leukotrienes, doses, age, duration of intervention, and lung function could not be assessed. Clearly, these preliminary conclusions may be modified with accumulating data from future well designed, parallel group, long term (> 20 weeks) randomised controlled trials; a prolonged (> 16 weeks) dose optimisation period before randomisation and intention to treat analysis are key design features to clarify the glucocorticoid sparing effect of anti-leukotrienes. Updates of this review will be available in the Cochrane Library.

What is already known on this topic

Anti-leukotrienes are increasingly being used as add-on therapy to inhaled glucocorticoids

No systematic review of randomised controlled trials has examined the evidence to support this treatment strategy

What this study adds

There is a shortage of relevant trials testing anti-leukotrienes at licensed doses as add-on therapy to inhaled glucocorticoids in patients, particularly children

Adverse effects

Montelukast at licensed doses was not associated with increased adverse effects. The 2.5-fold increased risk of serious adverse events, noted only in the tapering protocol in association with licensed doses of zafirlukast, raises concerns. Although the definition of serious events included those resulting in major disability, admission to hospital or prolongation of hospital stay, life threatening reaction, or death, the observed events were often linked with increased concentrations of liver enzymes prompting withdrawals (C Miller, personal communication, 2000). The fivefold increased risk of liver enzyme concentrations being increased and threefold increased risk of withdrawals owing to adverse events noted with higher than licensed doses of zafirlukast plead against using these drugs beyond the recommended doses. Other than the expected increased risk of oral moniliasis with double doses of inhaled steroids, no trials have examined important adverse effects associated with the prolonged use of inhaled glucocorticoids, such as osteopenia, adrenal suppression, and growth suppression in children; such documentation would have permitted a fairer comparison between the safety profile of the two treatments.

Conclusions

The addition of licensed doses of anti-leukotrienes to inhaled glucocorticoids may modestly improve the control of asthma. There is little evidence to consider their use as a substitute to increasing the dose of inhaled glucocorticoids. In well controlled patients, the addition of anti-leukotrienes is possibly associated with superior asthma control after glucocorticoid tapering, but there is insufficient evidence to quantify the corticosteroid sparing effect. Extrapolation of data to children remains speculative. Until further evidence is available, the gold standard of asthma treatment should remain the use of inhaled glucocorticoids at the lowest effective dose.

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Endpiece

Make the first move

Bully the [girls] first and they may not get to the point of bullying you, which, given a chance, they will certainly do.

Robertson Davies (1913-95), *What's bred in the bone*, London: Penguin, 1986