Pharmacotherapy — first-line maintenance therapy

Recommendations

First-line maintenance therapy

1. Physicians should recommend inhaled corticosteroids (ICSs) as the best option for anti-inflammatory monotherapy for childhood asthma (level I).
2. There is insufficient evidence to recommend leukotriene receptor antagonists (LTRAs) as first-line monotherapy for childhood asthma (level I). For children who cannot or will not use ICSs, LTRAs represent an alternative (level II).

Treatment of intermittent asthma with ICSs

3. There are insufficient data for physicians to recommend short courses of high-dose ICSs in children with mild, intermittent asthma symptoms, and the safety of these drugs has not been established (level II).
4. Physicians must carefully monitor children with intermittent symptoms to ensure that they do not develop chronic symptoms requiring maintenance therapy (level IV).
5. Physicians should recommend that children with frequent symptoms, severe asthma exacerbations or both receive regular, not intermittent, treatment with ICSs (level IV).

Add-on therapies

6. Long-acting β_2-agonists are not recommended as maintenance monotherapy in asthma (level I).
7. After reassessment of compliance, control of environment and diagnosis, if asthma is not optimally controlled with moderate doses of ICS, physicians may conduct a therapeutic trial of leukotriene receptor antagonist or long acting β_2-agonist as add-on therapy for any individual child (level IV).

ICSs are the most potent anti-inflammatory agents for the long-term management of asthma and their use as first-line agents is recommended in international guidelines.[1] It is important to consider that corticosteroids do not fully suppress the production or release of all inflammatory mediators including the cysteinyl leukotrienes.[2] Anti-leukotrienes have the advantage of being administered orally in a single or twice-daily dose and, as they are non-steroidal, may lack the adverse effects on growth, bone mineralization and the adrenal axis associated with long-term ICS therapy.

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Literature review (LTRAs for monotherapy in children)

A literature search was performed to identify any new trial or review article examining the safety and efficacy of anti-leukotrienes compared with placebo or other anti-asthmatic agents in childhood asthma. Trials comparing anti-leukotrienes to ICSs were identified by searching MEDLINE (1966–2003), EMBASE (1980–2003), CINAHL (1982–2003) and reference lists of systematic and narrative review articles and trials. We contacted international headquarters of anti-leukotriene producers to identify additional, pertinent, unpublished studies. The Cochrane Airways Group register of randomized controlled trials in asthma was searched using the following terms: (leukotriene* OR anti-leukotriene* OR leukotriene* antagonist* OR *lukast) AND [inhaled steroids*,beclomethasone*, fluticasone*, budesonide*, triamcinolone*). The searches were updated to February 2003.

Pertinent data published through to December 2004 were reviewed. There were insufficient data to modify the recommendations, but these data may serve as the focus of a subsequent case report with a discussion of the advantages and disadvantages of using LTRAs in the young child.

Current evidence

In Canada, only 2 preparations of anti-leukotrienes are available and both are LTRAs: montelukast, administered orally once daily in the evening (4-mg chewable tablets for children aged 2–5 years, 5-mg chewable tablets for children aged 6–14 years and 10-mg tablets for children aged 15 years and over) and zafirlukast, administered orally at a fixed dose of 20 mg twice daily on an empty stomach (licensed for children aged 12 years and older and adults).

LTRAs versus placebo

Four randomized controlled trials examined the efficacy of LTRAs compared with placebo in the pediatric population.[3–6] Among preschool-aged children, 2 randomized, double-blind, parallel trials compared montelukast to placebo. Knorr and colleagues[3] studied 689 children, aged 2–5 years, with mild persistent asthma who received either montelukast, 4 mg once daily at bedtime, or placebo for 12 weeks. Most children had activity-induced asthma (79%), abnormal radio-allergosorbent test (RAST) (49%) or both. Montelukast or placebo was administered in addition to ICSs in 28% of patients, in addition to cromolyn in 12%

and as monotherapy in the remainder. No subgroup analyses were provided to allow assessment of the efficacy of montelukast as monotherapy. Overall, when used either as an add-on or monotherapy, montelukast was found to be significantly more effective than placebo in terms of a number of outcomes, including days without asthma (64% v. 59%, $p = 0.01$); reduction in asthma symptoms (37% v. 26%, $p = 0.003$); days with β_2-agonist use (49% v. 55%, $p = 0.001$), use of rescue oral steroids (19% v. 28%, $p = 0.008$), but was not significantly more effective in reducing the number of patients with 1 or more exacerbation (26% v. 32%, $p = 0.10$). The number of patients who did not complete the study was similar in both groups (10% in the montelukast group; 11% in the placebo group). The effect of montelukast was evident within 1 day of starting therapy.

A second trial[4] tested 549 children aged 2–5 years with frequent episodic viral-induced asthma, with or without persistent symptoms. Montelukast, 4 mg once daily at bedtime (5 mg in those who became 6 years old during the study), was compared with placebo in a 12-month, parallel-group, randomized double-blind trial. Children treated with montelukast experienced 32% (95% CI 17–44) fewer exacerbations (defined as asthma and need for ≥2 doses/day of rescue β_2-agonists, for at least 3 consecutive days or use of rescue oral or inhaled steroids or hospital admission for asthma) than children receiving placebo (1.60 and 2.34 exacerbation/year, respectively). There were significantly ($p < 0.005$) more withdrawals from the study due to adverse events in the placebo group ($n = 30$, 11.1%) than in the treatment group ($n = 19$, 6.8%).

Two randomized, placebo-controlled, parallel-group, double-blind trials addressed the efficacy of LTRA in school-aged children. Knorr and colleagues[5] studied 336 children aged 6–14 years with mild-to-moderate asthma and an average FEV_1 of 72% of the predicted value. The overwhelming majority of the children had exercise-induced asthma (94%) or allergic rhinitis (92%). Montelukast (5 mg/day) or placebo was administered for 8 weeks as monotherapy in 74% of the children or in addition to ICSs in 36% of the children. Compared with placebo, montelukast is associated with significantly greater improvements in FEV_1 over the baseline measure (8.2% v. 3.6%, $p < 0.001$), reduction in the use of β_2-agonist (–0.6 v. –0.2 puffs/day), improved quality of life (symptoms, activity and emotions), reduction in serum eosinophils (–0.05 v. 0.01 × 10^9/L, $p = 0.02$), fewer days with an asthma exacerbation (20.6% v. 26.7%, $p = 0.5$) and fewer patients with an asthma exacerbation (84.8% v. 95.5%, $p = 0.002$). However, there was no difference between the groups in terms of change from baseline in morning PEFR (8.55 v. 6.14 L/minute, $p = 0.4$), nocturnal awakenings (–1.24 v. –0.95 nights/week, $p = 0.5$) daytime asthma symptom score (–0.16 v. 0.09, $p = 0.27$) and use of rescue oral steroids (12.1% v. 15.8%, $p = 0.4$).

In another report[6] of 2 trials involving children aged 5–11 years with mild to moderate asthma, zafirlukast administered as monotherapy twice daily for 6 weeks was compared with placebo. Although the study looked at 4 doses of zafirlukast (5 mg, 10 mg, 20 mg or 40 mg), the report focuses on the 411 children who received 10 mg twice daily (the approved pediatric dosage in the United States) or placebo. Zafirlukast significantly increased the change from baseline in percent predicted FEV_1 (9.8 v. 6.2 L, $p = 0.04$), morning PEFR (8.9 v. 3.9 L/minute, $p = 0.003$) and reduced the use of rescue β_2-agonist (–0.8 v. –0.4 puffs/day, $p = 0.02$) compared with placebo. There was no significant reduction in night awakenings (–0.6 v. –0.3 nights/week, $p = 0.14$) or any difference between the groups in withdrawal rate due to poor asthma control (2% v. 4%, not significant).

Several placebo-controlled trials[7,8] of adults and children aged 12 years and older also support the superiority of LTRAs in improving lung function and other indices of asthma control compared with placebo.

In summary, there is strong evidence derived from well-designed, randomized controlled trials that LTRAs are more effective than placebo in controlling persistent mild to moderate asthma in children aged 2–17 years.

LTRAs versus other non-steroidal agents (i.e., cromoglycate)

Two randomized, open-label, crossover trials[9,10] compared LTRAs and cromoglycate in school-aged children with asthma. Volovitz and associates[9] examined preference, satisfaction and adherence to treatment of 266 children aged 6–11 years with mild to moderate persistent asthma and a baseline FEV_1 of 74% of the predicted value. Children received oral montelukast (5 mg) at bedtime or cromolyn (2 mg 4 times daily via metered-dose inhaler [MDI]) for 4 weeks, separated by a 2-week wash-out period. Montelukast was preferred over inhaled sodium cromoglycate by 88% v. 12% ($p < 0.001$) of parents and by 80% v. 20% ($p < 0.001$) of children. Furthermore, satisfaction expressed by both parents and children was significantly higher for montelukast than sodium cromoglycate. Full adherence to therapy was greater with montelukast (≥95%) than sodium cromoglycate (85% v. 48%, $p < 0.001$). Use of rescue β_2-agonist was lower with montelukast than cromoglycate (1.05 v. 1.44 puffs/day, $p = 0.001$)

In another study by Volovitz and associates,[10] 23 children aged 6–11 years with moderate-to-severe asthma were treated with either montelukast (5 mg at bedtime) or cromolyn (2 mg 4 times daily) by MDI for 4 weeks with a 2-week washout period. The focus of the trial was the impact of treatment on the concentration of leukotrienes and eosinophilic cationic protein (ECP) in nasal washes. Most children (74%) had been using inhaled steroids before the study. Participants had a baseline FEV_1 of 73% predicted after a 2-week run-in with no medication. After 4 weeks of treatment, montelukast reduced the concentration of leukotrienes and ECP in the nasal washes. These effects were not observed when the same children were treated with cromolyn.

There is good evidence to support the higher parent and child satisfaction and adherence to treatment with once-daily oral LTRA compared with 4-times-daily inhaler. The evidence for clinical superiority is only supported at present by a lower use of rescue β_2-agonist with LTRA in school-aged children with persistent mild to moderate asthma.

LTRAs versus inhaled steroids

To date, 3 randomized trials have compared the efficacy of LTRAs and ICSs as monotherapy in children and have been summarized in a Cochrane review.[11] Two small well-designed, double-blind trials compared triamcinolone, 400 µg/day (i.e., 200 µg/day of chlorofluorocarbon [CFC] propelled beclomethasone equivalent) with montelukast, 5 mg (10 mg for children aged ≥15 years) in children aged 9–17 years with moderate persistent asthma. In the first,[12] 37 children were treated for 4 weeks. Both triamcinolone and montelukast improved FEV_1 (by about 500 mL or 22%) and clinical asthma score and decreased serum ECP and eosinophil counts. There was no significant difference between groups in these measures; however, the increase in serum IL-10 (an inhibitor of pro-inflammatory cytokine production) was significantly greater with triamcinolone than montelukast. The second trial[13] examined 55 children also treated for 4 weeks. Both triamcinolone and montelukast improved FEV_1 (by about 500 mL or 23%) and symptoms and decreased serum ECP and eosinophil counts with no significant group differences. A larger but methodologically weaker study by Maspero and collaborators[14] addressed the adherence, satisfaction and safety of montelukast. This trial was a 6-month open-label extension of a primary study comparing montelukast with cromoglycate where there had been a 54% dropout from the primary study. Although children were rerandomized for the extension study, the risk of an important selection bias of participants cannot be excluded. This unblinded trial involved 124 school-aged children (mean age 10 years) with mild asthma (mean baseline FEV_1 82% of predicted) assigned to montelukast, 5 mg once daily, or beclomethasone, 300 µg/day, for 24 weeks. The trial did not reveal a significant difference in risk of exacerbation (relative risk [RR] 0.8, 95% CI 0.3–1.9), nor in change in FEV_1 after 24 weeks of treatment (weighted mean difference [WMD] = –10 mL, 95% CI –140–120 mL). Because of insufficient power, these observations did not prove equivalence.

The Cochrane review[11] examined the combined effect of these 3 trials. The risk of experiencing an exacerbation requiring systemic steroids was not different between the groups nor was the rate of withdrawal due to poor asthma control; however, the power of these studies is insufficient to show equivalence. The change from baseline FEV_1 after 4 weeks of treatment revealed no group differences, but the need for rescue β_2-agonists was markedly lower in the group treated with inhaled steroids than among those using LTRAs.

Another trial[15] involved both adults and an unspecified number of adolescents aged 12 years and older with moderate asthma (mean baseline FEV_1 69% of predicted). Zafirlukast, 20 mg twice daily, was compared with fluticasone propionate, 200 µg/day, for 12 weeks. In this randomized double-blind controlled trial, the use of inhaled steroids resulted in a significant additional 240-mL (95% CI 110–370 mL) change in FEV_1. The risk of exacerbations was significantly greater (RR 2.7, 95% CI 1–7) in patients treated with LTRAs.

In conclusion, the evidence derived from 2 methodologically strong trials suggests equivalence of montelukast and 200 µg/day of beclomethasone-equivalent with regard to change in FEV_1; inhaled steroids are superior in reducing the need for rescue β_2-agonist use. These findings are consistent with those of a 2003 Cochrane review[16] of 13 (12 adult; 1 pediatric) trials demonstrating that 400 µg/day of CFC-propelled beclomethasone or equivalent are superior to montelukast, 10 mg/day, or zafirlukast, 20 mg twice daily. With all pediatric studies testing montelukast against inhaled steroids, it is impossible to comment on the efficacy of zafirlukast in pediatrics and on the relative potency of montelukast and zafirlukast in children.

Safety of LTRAs

Compared with placebo or non-steroidal anti-inflammatory drugs (NSAIDs), LTRAs are generally safe and well tolerated. Most clinical trials in children have consistently shown a low incidence of mild adverse events compared with placebo, cromolyn and nedocromil sodium. Since zafirlukast is metabolized in the liver through the P450 system, it may interfere with the metabolism of certain other drugs that use the same pathway. Although an association between LTRAs and Churg-Strauss syndrome has been observed in adults, to date there have been no reports of this in children.[17,18]

The overall risk of adverse effects appeared similar in children treated with anti-leukotrienes versus inhaled steroids in pediatric randomized controlled trials,[3,5,6] but the poor reporting and short duration of 2 of the 3 trials prevent total reassurance. Furthermore, adverse effects typically associated with inhaled steroids, such as growth suppression, osteopenia and adrenal suppression, were not measured, thus preventing a fair comparison of the safety of long-term use of inhaled steroids versus anti-leukotrienes. Although most of the evidence for efficacy is derived from randomized controlled trials, this design is inadequate to identify rare side effects, which are best assessed by post-marketing surveillance. Furthermore, there is insufficient experience with these drugs to assess the possibility of long-term side effects.

Alternatives to LTRAs

Two new Cochrane reviews[19,20] are shedding light on the

efficacy of inhaled sodium cromoglycate and ketotifen as alternatives to LTRAs and ICSs, although the mechanism of action of these medications has not been completely elucidated. Ketotifen is an H_1-receptor antagonist with some inhibitory effects on the allergic response. Cromoglycate partly inhibits IgE-mediated mast cell activation and has some suppressive effect on other inflammatory cells.

Cromoglycate is recommended as a second-line alternative to inhaled steroids as monotherapy for the treatment of asthma in several national and international consensus statements.[1,21–25] A Cochrane review[19] combined 24 randomized controlled trials, dating to November 2002, comparing inhaled sodium cromoglycate with placebo as monotherapy in children of all ages and confirms a previous meta-analysis published by the same group.[26] It reveals no group difference in the proportion of symptom-free days (WMD 3.57%, 95% CI –1.18%–8.32%) and in the use of rescue oral steroids (OR 0.76, 95% CI 0.34–1.72). However, a modest difference in the use of rescue bronchodilators was observed in favour of sodium cromoglycate with a reduction of 0.24 doses/day (95% CI 0.07–0.42 doses/day) and in overall symptoms (WMD 0.19, 95% CI 0.07–0.32). The authors conclude that, given the strong indication of publication bias, the small overall treatment effect and the pooled confidence intervals including zero for many outcome measures, recommending disodium chromoglycate as first-line maintenance therapy in childhood asthma cannot be justified.

A Cochrane review[20] of ketotifen examined 26 randomized, double-blind, controlled trials in children aged 4 months to 18 years. Ketotifen was given at a dose of 1 mg/day or more for 10–32 weeks as monotherapy or add-on therapy to various anti-asthmatic drugs (theophylline, ICSs, etc.). Compared to placebo, the proportion of children able to reduce or stop use of a bronchodilator within 12–16 weeks of treatment was significantly higher in the ketotifen group (RR 2.39, 95% CI 1.64–3.48, 4 trials). The beneficial effects of ketotifen were also evident in other outcomes. Reported side effects were more frequent in the ketotifen groups (sedation: 21%, weight gain: 27%) than in placebo groups (sedation: 12%, weight gain: 17%). The authors concluded that ketotifen alone or in combination with other interventions improves control of asthma and wheezing in children with mild and moderate asthma. This benefit is obtained at the cost of minor side effects, namely sedation and weight gain.

Implications for research

There is a paucity of high-quality, randomized controlled trials examining the various alternatives to inhaled steroids as monotherapy in mild asthma.

1. More pediatric trials, including those in preschool-aged children, are needed to compare the safety and efficacy of anti-leukotrienes versus inhaled steroids as single agents in the treatment of childhood episodic and persistent asthma. Long-term (>24–52 weeks) trials with adequate documentation of adverse effects associated with ICSs are needed to provide a fair comparison of the safety of both treatment options. To assess the dose-equivalence of anti-leukotrienes, trials in which ICSs are tapered to the minimum effective dose or trials testing the 200 µg/day beclomethasone-equivalent should be considered. The target population should be children with mild asthma (i.e., with normal lung function tests).
2. Head-to-head comparison of various anti-leukotrienes (particularly if zafirlukast is licensed for use in younger children) and of anti-leukotrienes versus inhaled cromoglycate and oral ketotifen are needed to determine the best second-line monotherapy for mild persistent asthma.
3. Future trials should be methodologically strong, i.e., double-blind, parallel-group, placebo-controlled, randomized controlled trials with complete reporting of withdrawals and dropouts, intention-to-treat analyses, careful reporting of important outcomes (exacerbations requiring systemic steroids, lung function tests, quality of life, use of rescue medication, etc.) and systematic documentation of adverse effects, including those associated with ICSs, such as oral candidiasis, osteopenia, adrenal suppression and growth suppression.

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