Stepping down from inhaled corticosteroids with leukotriene inhibitors in asthma: A systematic review and meta-analysis

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ABSTRACT

Background: The risks of using leukotriene receptor antagonists (LTRA) as part of a strategy for stepping down inhaled corticosteroid (ICS) are not well known.

Objective: To estimate the risk of asthma exacerbation in individuals with stable asthma who start LTRA when stopping ICS or reducing ICS dose.

Methods: We identified articles from a systematic review of English and non-English articles by using a number of data bases. We included randomized controlled trials with a stable asthma run-in period of 4 weeks or more and a follow-up period of at least 3 months. We included studies of individuals with stable asthma who stopped ICS and substituted LTRA (versus continuing ICS) and who reduced ICS while starting LTRA (versus placebo).

Results: The search strategy identified 1132 potential articles, of which 52 were reviewed at the full-text level, and four met criteria for inclusion. The single article that met the inclusion criteria for substitution of LTRA for ICS as a step-down strategy found a statistically increased risk of treatment failure of 30.3% for substituting LTRA compared with 20.2% for continuing ICS. The three articles that met the inclusion criteria for comparing LTRA versus placebo in patients with stable asthma who reduce ICS found a modestly decreased risk ratio that favored LTRA of 0.57 (95% confidence interval, 0.36–0.90; $I^2 = 0\%$) in studies that only included individuals >15 years old.

Conclusion: Only one study addressed the risk of substitution of LTRA for ICS in stable asthma, which limited any strong conclusions about this step-down strategy.

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Asthma is a prevalent chronic disease managed with ongoing adjustments of medications.¹ Authors of asthma treatment guidelines suggest that providers consider stepping down asthma medications when asthma is stable for 3 months.^{2,3} For individuals who have stable asthma on low-dose inhaled corticosteroid (ICS), one recommendation is to decrease the ICS dose by 25–50%.² Current guideline recommendations are based on limited data. Other options for individuals stable on low-dose ICS include stopping the ICS altogether with no substitute medication, stopping the ICS and substituting a leukotriene receptor antag-

onist (LTRA), reducing ICS while adding a LTRA, or using ICS on demand based on symptoms (or other parameters). Substituting LTRA or using LTRA to help reduce the ICS dose may be an attractive option for ease of use (tablet rather than inhaler form) and cost. Previous systematic reviews addressed the risks of asthma exacerbation when individuals stable on low-dose ICS stop⁴ or reduce ICS.⁵ Appreciation of these risks allows patients and providers to make informed decisions about stepping down asthma medicines. The goal of this systematic review was to identify randomized controlled trials (RCT) that compared the risk of asthma exacerbation on substituting LTRAs for ICS to the risk of continuing ICS in individuals with stable asthma. A second goal of the systematic review is to identify RCTs that compared the risk of asthma exacerbation when adding LTRAs to tapering ICS doses in individuals with stable asthma compared with adding placebo.

METHODS

Data Sources and Searches

This systematic review is consistent with the 27-item PRISMA statement checklist.⁶ We searched for RCTs with the study intervention of stopping ICS

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and substituting LTRA (or lipoxxygenase inhibitors) versus continuing ICS in individuals who were stable on low-dose ICS and for studies that involved tapering ICS along with LTRA or placebo. The search was assisted by an expert medical librarian (P.J.E.). We included studies that had a run-in period of at least 4 weeks with subjects on a stable dose of ICS to ensure a minimum period of asthma stability while participating in the trial. We recognize that 4 weeks is shorter than the 3 months of stability currently suggested by the most recent guidelines. We included studies with 3 or more months of follow-up after randomization to allow a reasonable time period to monitor for an asthma exacerbation to occur, although we recognize that a longer study period would likely detect additional events and provide even more information for a long-term risk estimate. There were no exclusions based on age or sex.

We performed a systematic review of English and non-English articles by using Ovid MEDLINE, Ovid EMBASE, Ovid CENTRAL, and Web of Science (inception to May 17, 2014). Search terms included anti-asthmatic agents, names for medication classes and for specific medications, and numerous descriptors for reducing medications (*e.g.*, step down, wean, withdraw, reduce). The MEDLINE search strategy was modified to accommodate the controlled vocabulary for EMBASE and CENTRAL; text words were used for the search performed in the Web of Science. In addition, we reviewed the reference sections of eligible studies and searched articles that had been cited by the eligible articles by using the Web of Science. We asked content experts for input about additional relevant studies or for any unpublished data pertinent to our research question. We used text words to search the following clinical trial registries for studies: clinicaltrials.gov, clinicaltrialregister.eu, and anzctr.org.au.

Study Selection

Two reviewers working independently and not blinded to the author(s), institution, or journal of publication determined the eligibility of the abstracts identified by using the search strategy. Full-text articles were obtained unless both reviewers determined that the abstract was ineligible for this study. For articles that could not be obtained in full text through the institution's interlibrary loan process and when disagreement existed between the two reviewers about advancing to the full-text review stage, a third reviewer assessed the abstract for criteria to advance to the full-text review stage. If two of the three reviewers recommended a full-text review, then additional efforts were made to obtain the full-text article. The full-text review was also performed in duplicate; disagreements about inclusion of full-text articles were

harmonized by consensus. If consensus was not reached, then arbitration by an additional content expert familiar with the predetermined inclusion and exclusion criteria was arranged.

Risk of Bias Assessment

We assessed the following study characteristics to judge the methodological quality of the included studies: how the randomization sequence was generated, how allocation was concealed, whether there were important imbalances in prognostic factors at baseline, which groups were blinded, and how missing outcome data were reported and analyzed. The risk of bias was assessed by using the Cochrane Collaboration risk of bias tool⁷ by two independent reviewers. Disagreements about risk of bias assessments were harmonized by consensus.

Data Synthesis and Analysis

We used a random-effects model to calculate the pooled relative risk ratio of an individual who experienced at least one asthma exacerbation if he or she used LTRA rather than placebo when reducing the ICS dose. We selected a random-effects model due to anticipated heterogeneity in how the outcome of asthma exacerbation was defined. We recorded how asthma exacerbation was defined for each included study. We measured inconsistency by using the I^2 test; higher I^2 scores indicated greater inconsistency. We used Review Manager 5.2 (Cochrane Collaboration) software to conduct the analyses.

RESULTS

Search Results

Our initial search strategy identified 840 articles. By using the additional strategies of reviewing the bibliography of the included studies, reviewing a list of studies that cited the included study, searching clinical trial registries, and contacting experts, we identified an additional 292 unique citations. Of the 1132 total unique citations, 54 met criteria for full-text review. Of the 54 full-text citations considered, four met criteria for inclusion.^{8–11} The PRISMA template⁶ for study selection is displayed in Fig. 1.

Substitution of LTRA for ICS as Step-Down Strategy

The study setting was multiple academic centers in North America. Individuals 6 years old and older participated in a 4–6-week run-in period on fluticasone diskus inhaler 100 μ g twice daily (beclomethasone 200 μ g/d equivalent), followed by randomization to continue the same fluticasone dose ($n = 165$) or substitute montelukast for 16 weeks ($n = 165$).

Figure 1. PRISMA flow diagram describing the steps of study selection. Source: Ref. 5.

Treatment failure was defined as any urgent medical visit for asthma, systemic corticosteroids, open-label use of ICS as determined by the provider, decrease in prebronchodilator forced expiratory volume in first second to more than 20% below baseline, decrease in peak flow rate to more than 35% below baseline on 2 consecutive days, use of >10 puffs of rescue β -agonist for 2 consecutive days, patient refusal to continue, or provider judgment for reasons of safety. The treatment failure rates were 20.2% in the continue ICS group and 30.3% in the LTRA group (hazard ratio 1.6; 95% confidence interval, 1.1–2.6) over the 16-week study period.

Use of LTRA or Placebo During ICS Dose Reduction

We identified three studies that met our inclusion criteria, all studies in adolescents and adults >15 years old who used montelukast 10 mg as the intervention.^{9–11} The ICS dose was reduced by 50% dose multiple times in two of the studies and not specified in the third study. Starting doses for ICS were specified in two of the studies, both of which were in the medium-high ICS dose range (beclomethasone equivalents

800–1600 μg for Tohda *et al.*,¹⁰ 400 μg for Riccioni *et al.*,¹¹ and not stated for Lofdahl *et al.*⁹). Asthma exacerbation definitions varied across the three studies. In Lofdahl *et al.*,⁹ failed rescue was defined as patients who were unstable and who failed to regain clinical stability after an increase in the dose of corticosteroids and also included withdrawal if a patient required treatment with systemic corticosteroid.⁹ In Tohda *et al.*,¹⁰ the patients were withdrawn from the study if asthma could not be controlled after increasing the dose of ICS. In Riccioni *et al.*,¹¹ we decided to count an asthma exacerbation if the dose of ICS could not be reduced due to worsening symptoms or if systemic corticosteroids were used. Study characteristics are summarized in Table 1.

Comparing LTRA versus placebo in patients with stable asthma when reducing ICS found a modestly decreased risk ratio that favored LTRA of 0.57 (95% CI, 0.36–0.90; $I^2 = 0\%$) (Fig. 2 a). One of the studies had a fixed ICS dosing schedule;¹¹ therefore, we compared only the two studies^{9,10} with flexible ICS schedules for final ICS dose and found no significant difference in standardized mean ICS dose at study conclusion, -0.03 (95% CI, -0.52 to 0.45 ; $I^2 = 83\%$) (Fig. 2 b).

Table 1. Summary of studies that considered use of LTRA to facilitate ICS tapering

Article	Setting	Country of Origin	Intervention	ICS Starting Dose	ICS Tapering Schedule	N-RX	N-Placebo	Ages (y)	Length of Run-in (wk)	Length of follow-up (wk)
Lofdahl 1999	Academic	US, Canada, Europe	Montelukast 10 mg	Not stated	Per-pre-set criteria every 2 weeks, 25% decrease	113	113	16–70	5–7	12
Tohda 2002	Academic	Japan	Montelukast 10 mg	Beclomethasone 800–1600 µg/d	50% at initiation and again at 8 and 16 wk per set criteria	93	98	16–70	4	24
Riccioni 2005	Academic	Italy	Montelukast 10 mg	Budesonide 800 µg/d	50% at 4, 8, and 12 wk	22	23	>15	4	12

Rx = treatment.

Figure 2. Meta-analysis for outcomes of using leukotriene receptor antagonist or placebo when tapering inhaled corticosteroid. (a) Asthma exacerbation. (b) Final ICS dose.

Risk of Bias

The risk of bias was assessed for each of the included studies, and these are summarized in Table 2. Notably, drop-out rates (not including those with treatment failure) for the trials that added LTRA for tapering ICS were 5% LTRA and 6% placebo for Tohda *et al.*,¹⁰ 5% for LTRA and 4% placebo for Riccioni *et al.*,¹¹ and 9% LTRA and 13% placebo for Lofdahl *et al.*⁹ There were concerns about high risks of bias in one of the included studies¹¹; therefore, the main outcome of asthma exacerbations was performed excluding this study yielding a similar conclusion (relative risk ratio 0.57; 95% CI, 0.36–0.90; $I^2 = 0\%$).

DISCUSSION

We performed a systematic review of RCTs with the intervention of substituting LTRA for ICS versus continuing the ICS and found only one trial that met our predetermined inclusion and exclusion criteria. Evidence for potential step-down methods for individuals who are currently stable on low-dose ICS is summarized in Table 3. The clinical implication of our findings is that the clinical trial evidence for estimating the risk of asthma exacerbation when substituting LTRA for ICS is low and is currently based on a single trial.

Although this may be an option that patients and providers continue to consider, we have more confident estimates in the risks for stopping ICS or reducing ICS, with the latter having a lower risk for future asthma exacerbations than the former.

We performed a second systematic review with a meta-analysis to estimate risk of reducing ICS with the addition of LTRA and found a modest risk reduction compared with placebo for the outcome of asthma exacerbation. Subjects in these studies started with a medium-high dose of ICS; therefore, these risk estimates are not directly comparable with the risks listed in Table 3. A similar analysis was performed by Ducharme¹² in a 2011 systematic review that considered multiple questions about the use of LTRAs for asthma. In their analysis, they included three articles that we did not include due to these articles not meeting our prespecified criteria for having a 4-week run-in period.^{13–15} Ducharme¹² identified four studies (two of montelukast and two of zafirlukast) that together showed no difference in ICS dose at study conclusion between the LTRA and placebo groups, similar to our findings. However, a significantly higher number of study withdrawals for poor asthma control was seen in the placebo group compared with the LTRA group as

Table 2. Risk of bias⁷ assessment for included studies

	Lofdahl 1999	Tohda 2002	Riccioni 2005	Peters 2007 ¹⁸
Random sequence generation	Low	Unclear	Unclear	Low
Allocation concealment	Unclear	Unclear	Unclear	Low
Blinding of participants and personnel	Low	Unclear	High	Low
Blinding of outcome assessment	Unclear	Unclear	High	Low
Incomplete outcome data	Unclear	Unclear	Unclear	Low
Selective reporting	Unclear	Unclear	High (symptoms not reported as outcome but described as being collected)	Unclear
Other bias	None identified	None identified	None identified	Baseline-level ICS before study enrollment higher in LTRA group (53% vs 40%)

Table 3. Evidence for options to step-down asthma treatment from low-dose ICS

Step-down method	No. RCTs	Relative Risk of an Asthma Exacerbation (95% confidence interval)*
Stop ICS ⁴	7	2.35 (1.88–2.92)
Reduce ICS dose ⁵	6	1.25 (0.96–1.62)
Substitute LTRA	1	1.6 (1.1–2.6)

*Compared with continuing a low-dose ICS

ICS doses were tapered, which indicates a possible modest ICS-sparing effect, similar to the modest effect we found with LTRA as reducing risk of asthma exacerbation.¹² Further supporting an overall role of LTRA in reducing risk of asthma exacerbation was a recently published systematic review and meta-analysis that found a reduced odds of asthma exacerbation of 0.60 (95% CI, 0.49–0.74) for LTRA compared with placebo.¹⁶ Despite slightly different inclusion-exclusion criteria and an updated search in this systematic review, we came to similar conclusions that adding LTRA allows slightly safer tapering of ICS in individuals >15 years old.

The main limitation of this systematic review was that only one study was identified that was pertinent to our research question about substitution of LTRA for ICS as a step-down strategy. This limits our ability to compare substitution of LTRA for ICS with other step-down strategies. Second, we found a small reduction in risk for asthma exacerbation when tapering ICS with LTRAs, which may be helpful when considering how

to taper from medium-high dose ICS. This strategy, however, would need to be compared directly with alternative strategies, *e.g.*, the addition of long-acting β -agonists. These conclusions must also weigh the potential risk of publication bias, which is difficult to estimate with only three included studies.^{9–11}

To summarize the findings from this systematic review, we included a summary table that uses the GRADE format (Table 4).¹⁷ The findings from this study could potentially further inform the Global Initiative for Asthma guideline recommendations on stepping down. Grade B evidence (a single high-quality RCT) against substituting LTRA for ICS is the only evidence we found in the systematic review for this step-down option. Grade A evidence (meta-analysis) of three studies of medium-high quality for adding LTRA^{9–11} during ICS taper could be considered so to increase the specificity of the current grade B recommendation for reducing ICS while adding other controllers; however, the asthma exacerbation risk reduction we found in this meta-analysis was modest and should only be applied to those >15 years old. Using a LTRA to substitute for ICS may still be a reasonable option for individuals based on a preference for a tablet over an inhaler, cost, or improved adherence. Decisions on how to best step down asthma medication remains individualized and requires discussion between the provider and the patient. More research, particularly clinical trials with interventions that use different step-down options, is needed so that patients and their providers have a stronger body of evidence to make informed decisions about stepping down asthma medication.

Table 4. Evidence summary when using the GRADE format¹⁷

Outcome	Intervention	Comparison	Risk Comparison	No. Participants	Quality of Evidence	Comment
Treatment failure (asthma exacerbation)	Substitution of LTRA = 20.2%	Continuation of ICS = 30.3%	Hazard ratio 1.6 (95% CI, 1.1–2.6)	<i>n</i> = 330	●●●○ (moderate, because of imprecision)	Did not separate children and adults
Treatment failure (asthma exacerbation)	Start LTRA during ICS taper = 11.0%	Placebo during ICS taper = 19.1%	Risk ratio 0.57 (95% CI, 0.36–0.90)	<i>n</i> = 439	●●●○ (moderate, because does not apply to all ages)	Only included >15 years old

CI = confidence interval.

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