Comparative Effectiveness Review
Number 194

Effective Health Care Program

Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

Executive Summary

Objectives and Rationale for the Review

This report summarizes a systematic review of intermittent inhaled corticosteroids and long-acting muscarinic antagonists for asthma, and identifies needs for future research. This was one of the six high priority topics within asthma identified by a National Heart, Lung, and Blood Institute Advisory Council Asthma Expert Working group.[1]

The objectives of the systematic review are:

- To assess efficacy of intermittent inhaled corticosteroid (ICS) therapy in different populations:
  - Patients 0 to 4 years old with recurrent wheezing
  - Patients 5 years and older with persistent asthma (with or without long-acting beta agonist (LABA)
- To assess efficacy of adding long-acting muscarinic antagonist (LAMA) to ICS with or without LABA in:
  - Patients 12 years and older with uncontrolled, persistent asthma.

Background

Scheduled, daily dosing of ICS is the preferred pharmacologic controller therapy for persistent asthma in patients of all ages.[1]

Purpose of Review

To assess the efficacy of intermittent inhaled corticosteroids in different populations of patients with asthma and to assess whether adding long-acting muscarinic antagonists improves outcomes for patients with uncontrolled, persistent asthma.

Key Messages

- In children less than 5 years old with recurrent wheezing, intermittent use of inhaled corticosteroids during an upper respiratory tract infection decreases asthma exacerbations.
- In patients 12 years and older with persistent asthma:
  - using inhaled corticosteroids intermittently may be as effective as using them as a controller medication.
  - using inhaled corticosteroids and long-acting beta-agonists together as controller and quick relief therapy reduces asthma exacerbations compared to using inhaled corticosteroids alone or with long-acting beta-agonists as a controller.
- In patients 12 years and older with uncontrolled, persistent asthma, adding long-acting muscarinic antagonists to:
  - inhaled corticosteroids reduces exacerbations and improves lung function.
  - inhaled corticosteroids and long-acting beta-agonist controllers improves asthma control and lung function.

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"Controller therapy" describes medications taken daily on a long-term basis to achieve and maintain control of persistent asthma.[2] Rather than being taken for immediate symptom relief, controller therapy is intended to reduce future exacerbations and the need for immediate symptom relief. In this report, controller medications are defined by the timing and indication for use rather than by mechanism of action.

"Quick relief" therapy describes medications used as needed upon onset of symptoms for acute symptom relief. Likewise, for this report, quick relief therapy is defined by the timing and indication for use rather than by mechanism of action.

Worsening control of asthma or other criteria may prompt changes in prescription therapy, such as intermittent dosing.

"Intermittent" dosing describes the use of medication that may vary in the dose, frequency, or duration of administration. Some examples of intermittent ICS dosing include initiating a temporary course of ICS or temporarily increasing the dose of ICS that is otherwise taken as controller therapy.

An extension of intermittent ICS therapy is the use of ICS and LABA as controller therapy both on a regular basis and on immediate symptom onset for quick relief therapy.[3]

LAMA represents a new pharmacologic class of long-acting bronchodilators that have been studied as a controller therapy for asthma. At least one LAMA has gained Food and Drug Administration (FDA) approval for the long-term maintenance treatment of asthma in patients 6 years and older.[4]

The review focuses on drugs as a class, as described in Table A.

Table A. Drugs included in the review

Class	Drugs
ICS	Beclomethasone,[a] budesonide,[a] ciclesonide,[a] Flunisolide,[a] fluticasone,[a] mometasone,[a] triamcinolone[b]
LABA	Arformoterol, formoterol,[a] olodaterol, salmeterol,[a] vilanterol,[a,c]
LAMA	Aclidinium, glycopyrrolate, tiotropium,[a] umeclidinium

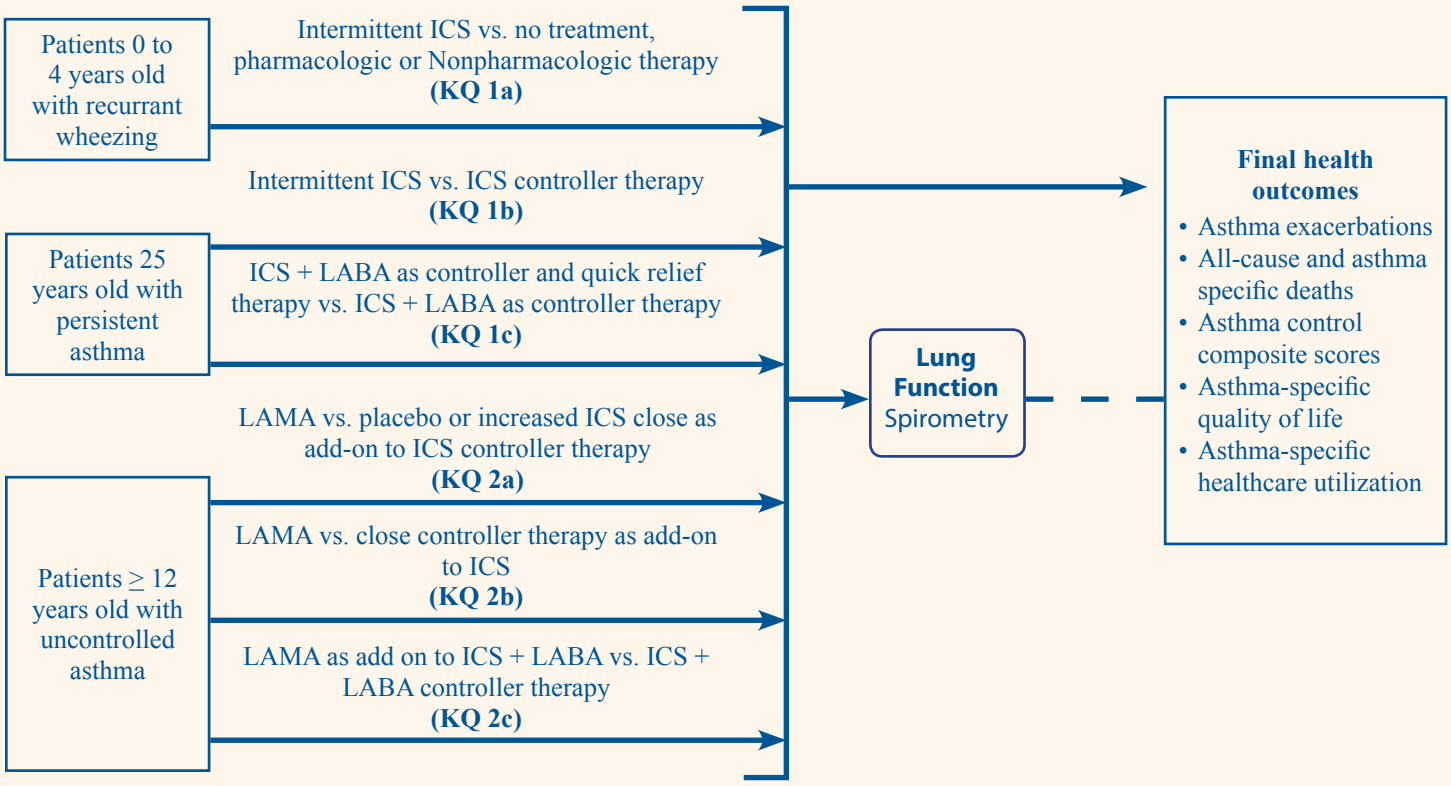
FDA = Food and Drug Administration; ICS = inhaled corticosteroid; LABA = long-acting □2-agonist; LAMA = long-acting muscarinic antagonist

[a] Currently with FDA approval for asthma, either as a single ingredient product or as a component of a multi-ingredient product.

[b] Previously FDA approved, although discontinued in 2010.

[c] Considered an ultra-long-acting □2-agonist.

Figure A. Scope of review



ICS = inhaled corticosteroid; KQ = Key Question; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist

Data Sources

Data sources were MEDLINE®, Embase®, Cochrane Central, and Cochrane Database of Systematic Reviews bibliographic databases from earliest date through March 23, 2017; hand searches of references of relevant studies; www.clinicaltrials.gov and the International Controlled Trials Registry Platform. The systematic review protocol is available in the full report.

Results

We found 56 unique studies (54 randomized controlled trials, 2 observational studies) in this review. Fifteen randomized controlled trials were specific to LAMA therapy in patients 12 years and older with persistent uncontrolled asthma. An overview of the results is presented in Tables B through E.

Table B. Results for patients 0 to 4 years of age with recurrent wheezing

Intervention	Effect
Intermittent ICS with SABA prn vs. SABA prn at the onset of a URI	• Reduces the risk of exacerbation requiring oral corticosteroids (moderate SOE) • Improves QOL (low SOE) • Does not affect: – Other measures of exacerbation (low or high SOE) – Rescue medication use (low SOE)
Intermittent ICS vs. ICS controller	• Does affect: – The risk of exacerbations requiring oral corticosteroids (low SOE) – Hospitalization (low SOE) – Rescue medication use (low SOE)
Intermittent ICS vs. no therapy	• No conclusion possible (insufficient SOE)
Intermittent ICS vs. nonpharmacologic therapy	• No conclusion possible (insufficient SOE)

ICS = inhaled corticosteroid; QOL = quality of life; SABA = short-acting beta agonist; SOE = strength of evidence; URI = upper respiratory infection

Table C. Results for patients 5 to 11 years of age with persistent asthma

Intervention	Effect
Intermittent ICS vs. ICS controller	• Does not affect: – QOL (low SOE) – Rescue medication use (low SOE) • No conclusion possible for other outcomes (insufficient SOE)
ICS combined with LABA as controller and quick relief vs. a higher ICS controller dose	• Reduces the risk of exacerbations measured as a composite outcome (low SOE)
ICS combined with LABA as controller and quick relief vs. ICS and LABA as controller at the same ICS dose	• Reduces the risk of exacerbations measured as a composite outcome (low SOE)

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; QOL = quality of life; SOE = strength of evidence

Table D. Results for patients 12 years of age and older with persistent asthma

Intervention	Effect
Intermittent ICS and ICS controller vs. ICS controller	• Does not affect the risk of exacerbations, regardless of definition (low SOE) • Decreases asthma-related outpatient visits (low SOE).
Intermittent ICS vs. ICS controller	• Does not affect: – The risk of exacerbation regardless of definition (low SOE) – Asthma control scores (low SOE) – Spirometry (low to high SOE) – QOL (moderate SOE) – Rescue medication use (moderate SOE)
ICS combined with LABA as controller and quick relief vs. the same ICS controller dose	• Reduces: – The risk of exacerbations defined as a composite outcome (moderate SOE) – Rescue medication use (low SOE) • Improves spirometry (moderate SOE)
ICS combined with LABA as controller and quick relief vs. a higher ICS controller dose	• Reduces the risk of exacerbations defined as a composite outcome (low SOE)
ICS combined with LABA as controller and quick relief vs. ICS and LABA as controller at the same ICS dose	• Reduces: – The risk of exacerbations defined as a composite outcome (high SOE) – Rescue medication use (low SOE) • Improves asthma control scores (moderate SOE)
ICS combined with LABA as controller and quick relief vs. ICS and LABA as controller at a higher ICS dose	• Reduces the risk of exacerbations defined as a composite outcome (high SOE)
ICS combined with LABA as controller and quick relief vs. conventional best practice of ICS with or without LABA as controller	• Reduces: – The risk of exacerbations defined as a composite outcome (moderate SOE) – Rescue medication use (moderate SOE) • Improves asthma control scores (moderate SOE)

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; QOL = quality of life; SOE = strength of evidence

Table E. Results for patients 12 years of age and older with uncontrolled, persistent asthma

Intervention	Effect
Adding LAMA to ICS vs. adding placebo	• Reduces the risk of exacerbations requiring systemic corticosteroids (high SOE) • Improves spirometry (high SOE) • Does not affect: – Asthma control scores (moderate SOE) – QOL (low to high SOE) – Rescue medication use (moderate SOE)
Adding LAMA to ICS vs. doubling ICS dose	• Does not affect: – The risk of exacerbations requiring systemic corticosteroids (low SOE) – Asthma control scores (low SOE) – Spirometry (low SOE) – QOL (low SOE)
Adding LAMA to ICS vs. adding LABA	• Does not affect: – The risk of exacerbations requiring systemic corticosteroids (low SOE) – Death (low SOE) – Asthma control scores (low to high SOE) – Spirometry (low to high SOE) – QOL (low to high SOE) – Rescue medication use (low SOE)
Adding LAMA to ICS and LABA vs. ICS and LABA	• Does not affect – The risk of exacerbations requiring systemic corticosteroids (moderate SOE) – Hospitalization (low SOE) • Improves – Asthma control scores (low to moderate SOE) – Spirometry (high SOE)

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; QOL = quality of life; SOE = strength of evidence

Discussion

This review evaluated different ICS dosing strategies and LAMA therapy in people of various ages with persistent asthma. Comparisons were class-based and thus this review does not inform the impact of specific doses on outcomes; rather, it more globally addresses classes and broad dosing strategies (i.e. intermittent dosing of ICS). Although effectiveness is an important part of decision-making, this report did not include harms associated with drug therapies, which should also be taken into consideration.

There is a relatively smaller amount of published evidence on intermittent ICS dosing as compared to the amount of evidence on combined ICS and LABA as quick relief and controller therapy or LAMA therapy. This lack of evidence should not be equated to lack of benefit necessarily. Given most outcomes were rated with low strength of evidence, future research could change the direction or magnitude of effect or the strength of evidence as the consistency and precision in effect estimates improve.

Conclusions

Compared to rescue SABA use, adding intermittent ICS use appears to benefit children less than 5 years old with recurrent wheezing in the setting of an RTI. In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence leading to primarily low strength of evidence ratings. Using ICS and LABA combined as both a controller and quick relief therapy showed benefits over use as a controller medication alone (ICS or ICS and LABA controller). In patients 12 years and older with uncontrolled, persistent

asthma, adding LAMA to ICS controller or ICS plus LABA controller compared to ICS or ICS plus LABA alone improves some outcomes. However, adding LAMA to ICS controller compared to adding LABA to ICS controller or increasing dosage of ICS controller did not improve outcomes.

References

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Full Report

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