

EXECUTIVE SUMMARY

Issue

In 2005, 2.25 million Canadians aged 12 years or older were diagnosed with asthma (approximately 8.3% of the general population aged 12 years or older). Patients with asthma reported symptoms or attacks daily (14%) or several times per month (37%).

The Canadian Asthma Guidelines recommend the use of inhaled corticosteroid (ICS) and rescue short-acting beta₂-agonist (SABA) agents in first-line medical management of chronic persistent asthma. The guidelines recommend add-on combination therapy of a long-acting beta₂-agonist (LABA) with an ICS after failure to gain adequate control with ICS monotherapy. There are variations among provincial public drug plans in the criteria for reimbursement that stem from concerns about clinical care and the sustainability of drug funding given limited resources.

Objectives

This project aimed to evaluate the clinical efficacy, safety, and cost-effectiveness of LABA-ICS combination therapy for adults (12 years of age or older) who are diagnosed with persistent asthma. To achieve these objectives, the following research questions were proposed:

- What is the clinical efficacy of LABA plus ICS maintenance therapy compared with ICS monotherapy in steroid-naïve patients with persistent asthma (ICS treatment-naïve) aged 12 years or older?
- What is the clinical efficacy of LABA plus ICS maintenance therapy compared with ICS monotherapy in patients with persistent asthma aged 12 years or older who are being treated with an ICS?
- What is the comparative efficacy of salmeterol-fluticasone versus formoterol-budesonide maintenance therapy in patients with persistent asthma aged 12 years or older?
- Are there differences in adverse events between combination LABA-ICS treatment (for example, inhaled salmeterol-fluticasone and formoterol-budesonide combinations) and ICS monotherapy?
- Is there evidence that adding a LABA to an ICS allows for a reduction in the ICS dose (do LABAs have a steroid-sparing effect)?
- What is the cost-effectiveness of LABA plus ICS maintenance therapy compared with ICS monotherapy for ICS-naïve patients and those uncontrolled on low- or medium-dose ICS monotherapy?
- What are the recommendations regarding LABA plus ICS use in Canadian, North American, and international (GINA) guidelines for the management of asthma?

Clinical Review

Methods: A systematic review was conducted to identify all randomized controlled trials (RCTs) that compared LABA-ICS with ICS monotherapy or another LABA-ICS combination therapy for the management of persistent adult asthma. Meta-analyses were performed when appropriate.

Results: Meta-analyses indicated that LABA-ICS has a clinically meaningful benefit compared with ICS monotherapy among steroid-naïve adults in improving morning peak expiratory flow (PEF) and increasing the number of symptom-free days (SFDs). Assuming a study control-group

risk of exacerbation of approximately 50%, the number needed to treat to prevent one exacerbation was four (95% CI 3 to 24). This was based on one trial of 12 weeks' duration.

Thirty-seven RCTs evaluated the efficacy of LABA-ICS therapy compared with that of similar-dose ICS monotherapy. Meta-analyses showed that the use of LABA-ICS may have a clinically meaningful benefit compared with ICS monotherapy in improving morning and evening PEF and increasing the number of SFDs and days with optimal control. Assuming a study control-group risk of exacerbation of 27%, the number needed to treat to prevent one exacerbation was 19 (95% CI 13 to 38).

Thirty-one RCTs evaluated the efficacy of LABA-ICS therapy compared with that of higher-dose ICS monotherapy. Meta-analyses indicated that the use of LABA-ICS may have a clinically meaningful benefit compared with ICS monotherapy in improving morning PEF, reducing the risk of an exacerbation and increasing the number of SFDs and days with optimal control. The results suggest that LABA-ICS is clinically equivalent to a higher-dose ICS in improving evening PEF, absolute and per cent-predicted forced expiratory volume in one second, reducing SABA use, and improving quality of life. Assuming a study control-group risk of exacerbation of 28%, the number needed to treat to prevent one exacerbation was 23 (95% CI 16 to 52).

Twelve RCTs evaluated the relative efficacy of various LABA-ICS therapies for adult persistent asthma. Meta-analyses indicated that there was no clinically meaningful benefit of using one LABA-ICS combination compared with another in improving pulmonary function, asthma symptom control, or health-related quality of life.

Twelve RCTs evaluated the potential steroid-sparing effects of LABA-ICS combination therapy compared with ICS monotherapy. Meta-analyses failed to indicate clinically meaningful differences between using LABA-ICS or ICS in any pulmonary function measures. The results suggest that a lower-dose LABA-ICS is equivalent to ICS in improving absolute and per cent-predicted forced expiratory volume in one second and reducing SABA use. The statistically significant differences favoured the use of LABA-ICS for an increase in SFDs and a reduction of mean ICS dose. Subgroup analyses indicated a statistically significant reduction in SABA use favouring the use of LABA-ICS for the step-down reduction of ICS. There was no clinically meaningful difference between the two treatments in health-related quality of life.

The safety of LABA-ICS combination therapy compared with that of ICS monotherapy was evaluated based on data from 79 RCTs. Among 10 key safety measures, worsening asthma was reduced by 22% (95% CI 34% to 10%) when LABA-ICS therapy was used. There were no statistically significant differences between the treatments for the remaining nine measures.

Economic Analysis

Methods: A systematic review of economic evaluations comparing the use of LABA-ICS combination therapy with ICS monotherapy in patients with asthma who were 12 years of age or older was conducted.

A Markov model was created to estimate the long-term costs and quality-adjusted life-years (QALYs) that were associated with four strategies relating to the optimum time to introduce

LABA in combination with ICS as initial therapy, after lack of control on low-dose ICS, after lack of control on medium-dose ICS, or after lack of control on high-dose ICS.

Results: The studies that were identified during the economic review had weaknesses in analysis, funding, and use of comparators. This supported the need for a full economic analysis from the Canadian context.

In comparing all four strategies, the incremental QALYs gained from introducing a LABA earlier are small at 12 weeks and one year. The total costs are higher the earlier a LABA is introduced. For treatment-naïve patients, the incremental cost per QALY gained from treatment with LABA plus ICS instead of ICS monotherapy is \$3.3 million. For asthma that is uncontrolled on low-dose ICS, the incremental cost per QALY gained from treatment with LABA plus low-dose ICS instead of medium-dose ICS monotherapy is \$1.6 million. For asthma that is uncontrolled on medium-dose ICS, the incremental cost per QALY gained from treatment with LABA plus medium-dose ICS instead of high-dose ICS monotherapy is \$190,000. The results were insensitive to changes in relevant parameters.

Health Services Impact

Based on data from British Columbia, in all scenarios, the forecasted expenditure for LABA-ICSs that are used by patients with asthma will increase during the next three years. Switching from the use of a low-dose LABA-ICS to a higher-dose ICS could produce cost savings of \$11,000 (0.1%) to \$44,000 (0.4%) per year. Switching from the use of a low- and medium-dose LABA-ICS to a higher-dose ICS could provide cost savings of \$125,000 (1.1%) to \$500,000 (4.6%) per year. If low- and medium-dose LABA-ICS combinations are switched to higher-dose ICS and patients on single-inhaler LABA-ICS therapy are given increased ICS, the cost savings range from \$270,000 (2.5%) to \$1.1 million (10%) per year. For these savings to be realized, it is necessary to delay the introduction of LABAs until a patient's asthma is uncontrolled on high-dose ICS monotherapy.

Conclusions

This review confirms that for most patients with persistent asthma, initial therapy and the only therapy that is needed is ICS. The LABA-ICS combination provides some benefit that is limited in the range of symptoms for which control is improved and in the clinical meaningfulness of the improvements. The efficacy and safety results suggest that there are often statistically significant but not clinically meaningful benefits from switching to combination therapy for the management of most asthma that is not controlled by the use of ICS. For asthma that is controlled on ICS, the addition of a LABA may help to reduce the amount of daily ICS used and may thereby reduce the risk that is associated with prolonged use of daily high- and moderate-dose ICS. In addition, the number and severity of exacerbations can be reduced with this management strategy. There are no clinically important differences between LABA-ICS combination therapies.

The cost-effectiveness analysis suggests that the introduction of a LABA before patients have tried high-dose ICS monotherapy may not be justified. The later a LABA is introduced into therapy, the more cost-effective the strategy becomes. The optimum strategy among the four that were considered occurred when patients started using a LABA after their asthma was uncontrolled by high doses of ICS. A sensitivity analysis revealed that these results were insensitive to changes in relevant parameters.