Issues in Emerging Health Technologies

Role of Combination Inhaled Corticosteroids and Long Acting Beta Agonists in the Treatment of Adult Asthma

Summary

✓ An inhaled corticosteroid (ICS) and a long acting beta agonist (LABA) are combined in an inhaler for treatment of persistent asthma.

✓ There is evidence that maintenance therapy with a combination ICS/LABA inhaler improves clinical outcomes and reduces airflow obstruction in patients with persistent asthma, who are not well controlled even when using ICS maintenance therapy. There is evidence that a combination ICS/LABA inhaler may also play a role in initial maintenance therapy for patients with mild persistent asthma, who have never used ICS therapy. There is no evidence regarding the use of combination therapy in intermittent asthma.

✓ Oral candidal infections, hoarseness and pharyngolaryngeal pain are the most frequently reported adverse events.

✓ Combination inhaler therapy can improve compliance with guidelines that recommend a LABA only be used with concurrent ICS administration.

The Technology

ICS are anti-inflammatory agents that are used in primary pharmacotherapy for mild persistent asthma. Canadian asthma guidelines recommend the addition of bronchodilating maintenance therapy in the form of a LABA, if asthma symptoms are poorly controlled on low dose ICS alone. ICS/LABA fixed dose combinations in one inhaler are available as fluticasone/salmeterol (Advair®, GlaxoSmithKline) or budesonide/formoterol (Symbicort®, AstraZeneca).

Regulatory Status

Advair® is approved in Canada, the US and the UK for the treatment of asthma. Symbicort® is approved for the treatment of asthma in Canada and the UK, but is not yet approved in the US.

Patient Group

Asthma is defined by paroxysmal or persistent symptoms of chest tightness, cough and wheeze. The pathophysiology includes reversible airway smooth muscle constriction and inflammation that may lead to airway remodelling. The Global Initiative for Asthma (GINA) guidelines, which were developed by the National Institutes of Health and the World Health Organization, with financial support from the pharmaceutical industry, grade asthma severity as intermittent, mild persistent, moderate persistent and severe persistent.

The prevalence of asthma in Canada in 1998 to 1999 was 7.5% for adults. Unscheduled asthma treatments in emergency departments accounted for 18% to 28% of patient visits during a 12-month period.

Current Practice

Drugs that are used to treat asthma are rescue medications or control medications. Short acting beta agonists (rescue medication) are used intermittently to treat acute symptoms. ICS (controller medication) are used regularly to reduce airway inflammation. Canadian guidelines, which were also sponsored by industry, recommend that an ICS be added to rescue medication for patients with mild persistent asthma. The Canadian guidelines recommend the addition of a LABA for patients who are not controlled on low dose ICS alone, but exclude...
the initiation of combination inhaler therapy for patients with mild persistent asthma.2,4

A retrospective study shows that between 1997 and 1998, 15% of patients in Quebec who filled a prescription for a LABA concurrently filled a prescription for ICS.5 Over-reliance on rescue medication or on LABAs without appropriate ICS maintenance therapy is common. A review of British Columbia prescriptions (1996 to 1998) shows that compliance with guideline recommendations is worsening.6 "There is better guideline adherence among patients receiving a combination ICS/LABA inhaler."7

The Evidence

Three randomized controlled trials (RCT) influenced the use of LABA therapy in asthma. These were the Formoterol and Corticosteroids Establishing Therapy (FACET) study,8 the Oxis and Pulmicort Turbuhaler In the Management of Asthma (OPTIMA) study9 and the Gaining Optimal Asthma control (GOAL) study.10 These high quality studies used a composite endpoint (severe exacerbation) that incorporated treatment with oral corticosteroids,8-10 emergency department visits9,10 and hospitalizations.8-10

FACET8 examined 423 patients who were taking regular ICS and compared patients receiving both LABA and ICS to those receiving ICS only during a 12-month period. One primary endpoint was the annual rate of severe exacerbations [defined as a need for oral corticosteroid or a decrease in morning peak expiratory flow (PEF) by 30% on two consecutive days]. This rate was 0.91 per patient annually in the ICS group and 0.67 per patient annually in the ICS/LABA group (p=0.01). Other endpoints (e.g., symptom scores, nocturnal awakenings, PEF) were significantly improved in the ICS/LABA group compared with the group on ICS alone. This study showed that adding a LABA to an ICS was beneficial in a population with an asthma severity equivalent to mild persistent to moderate persistent asthma.

OPTIMA also tested patients who had not received ICS in the preceding three months (steroid naïve). These patients were randomized to receive placebo (n=239), ICS (n=228) or a combination ICS/LABA inhaler (n=231). During one year, placebo patients experienced more frequent severe exacerbations (0.77 per patient annually) than the ICS group (0.29 per patient annually) or the ICS/LABA group (0.34 per patient annually). There was no advantage in adding a LABA to ICS therapy in steroid naïve patients. Based primarily on these findings, the Canadian Asthma Guideline Committee excluded initial maintenance combination treatment in those with mild asthma or in steroid naïve patients.4

FACET,8 OPTIMA9 and other studies11-13 show that adding a LABA to ICS is clinically beneficial for moderate persistent asthma (defined by the presence of daily symptoms, exacerbations that may affect activity and sleep, nocturnal symptoms at least weekly and impaired objective measures of airflow).

GOAL tested the efficacy of a combination fluticasone/salmeterol (n=548) as initial therapy against that of fluticasone (n=550) alone during one year.10 A subset of steroid naïve patients was included. The primary endpoint, well controlled asthma, was achieved in 78% and 70% of steroid naïve patients in the ICS/LABA and the ICS groups respectively (p=0.003). Total control was achieved in 42% and 31% of the steroid naïve patients in the ICS/LABA and the ICS groups respectively (p<0.001). Other clinical endpoints (e.g., exacerbation rates) also favoured the ICS/LABA combination compared with ICS alone. As a result, GOAL indirectly supports the use of combination ICS/LABA as initial maintenance therapy for steroid naïve patients.

Three other RCTs support the use of combination ICS/LABA for initial management in mild asthma14 or in steroid naïve15,16 patients. These studies are of lower quality. Even with their limitations, these studies show that those with mild asthma experience improved morning and evening PEF, lower exacerbation frequency and longer time to first exacerbation with the budesonide/formoterol combination (n=230)
compared to double the budesonide dose (n=237). Steroid naïve subjects have better surrogate outcomes with combination ICS/LABA compared to individual monocomponents.

**Adverse Effects**

Drug related adverse events include oral candidal infections, hoarseness and pharyngolaryngeal pain. Headache, tremor, tachycardia and gastrointestinal upset were infrequently noted. Class specific adverse events (tachycardia and tremor) occurred in 2% to 3% of patients. Lung function can deteriorate and the frequency of asthma exacerbations can increase with the repeated use of salbutamol (a short acting beta-2 agonist) in some patients, depending on their genetic profile. With the expanded maintenance use of a LABA, there is a need to investigate the adverse responses associated with chronic beta-2 agonist stimulation. Also, the markers of inflammation may be elevated in patients on combination ICS/LABA compared with patients on a higher dosage of ICS alone. An ICS dose can be reduced when ICS and LABA are used in combination while maintaining symptom control and exacerbation reduction. As a result, the clinical significance of ongoing inflammation despite good clinical control should be evaluated.

**Administration and Cost**

GlaxoSmithKline markets Advair® as 100/50 micrograms, 250/50 micrograms or 500/50 micrograms dry powder inhalers of fluticasone/salmeterol (Diskus®) and 125/25 and 250/25 fluticasone/salmeterol in metered dose inhalers. The unit cost for these products varies from $77.80 to $132.16, depending on the strength. The supply is expected to last for an average of one month.

AstraZeneca markets Symbicort® as 100/6 micrograms or 200/6 micrograms of budesonide/formoterol dry powder inhaler (Turbu-haler®). Unit costs for these products are $65.10 and $84.63 respectively. The supply is expected to last for an average of one or two months.

**Concurrent Development**

Other treatments for asthma have become available (i.e., omaluzimab, a monoclonal antibody that blocks the interactions between IgE and receptors on mast cells and basophils); or may soon become available (e.g., roflumilast, a specific PDE4 inhibitor). There are extensive human data regarding the roles of ICS and LABA and it is unlikely that ICS or ICS/LABA combinations will be replaced in the short term.

**Rate of Technology Diffusion**

Several factors may positively influence the endorsement of combination ICS/LABA inhalers. Advair® and Symbicort® achieved recognition among Canadian patients and physicians, because of marketing and physicians’ involvement in large Canadian clinical trials. These medications are simple for physicians to prescribe and for patients to use. There is potential for off-label prescription, as has likely occurred in Quebec, with these inhalers becoming a panacea for patients with symptoms of cough, dyspnea or chest tightness.

**Implementation Issues**

The primary limitation to the rapid uptake of combination inhalers is cost. Two analyses, based on economic modelling, suggest that combination ICS/LABA therapy is cost-effective compared with ICS monotherapy in a subset of patients. A formal economic analysis comparing treatment with combination ICS/LABA inhalers to treatment with ICS inhalers and LABA inhalers is unavailable. Until such an evaluation is done, the relative value of combination ICS/LABA inhalers in mild persistent asthma is unknown.

Combination ICS/LABA inhaler therapy has theoretical clinical and proven compliance benefits. Substituting a combination ICS/LABA inhaler for two separate inhalers will ensure that the LABA is not taken in isolation and can result in improved outcomes.

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improves clinical outcomes and reduces airflow obstruction in patients with persistent asthma, who are not well controlled even when using ICS maintenance therapy. There is evidence that combination ICS/LABA inhalers may play a role in initial maintenance therapy for patients with mild persistent asthma, who have never used ICS therapy. There is no evidence for combination therapy in intermittent asthma.

References


Cite as: Mayers I, Damant R. Role of combination inhaled corticosteroids and long acting beta agonists in the treatment of adult asthma [Issues in emerging health technology issue #]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.

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CCOHTA takes sole responsibility for this bulletin and appreciates comments from its reviewers.

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*Dr. Ducharme has received fees from AstraZeneca, Boeringher Ingelheim, GlaxoSmithKline, Novartis and Merck Frosst.
†Dr. FitzGerald has received funding from AstraZeneca and GlaxoSmithKline.

Production of this report is made possible by a financial contribution from Health Canada’s Health Care Strategies and Policy, federal, provincial and territorial partnership grant program.

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