Should combination therapy with inhaled corticosteroids and long-acting β_2-agonists be prescribed as initial maintenance treatment for asthma?

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In March of this year, GlaxoSmithKline (GSK) received approval from Health Canada for a revised product monograph with a new indication for the use of Advair, an aerosol containing both salmeterol, a long-acting β_2-agonist, and fluticasone, an inhaled corticosteroid for use in patients with asthma. The new monograph states that "Advair … is indicated for the maintenance treatment of asthma in patients … where the use of a combination product is considered to be appropriate" (www.gsk.ca/en/products/prescription/ [Note: the product monograph may be accessed by clicking on the Advair logo]). The company began a marketing campaign, approved by the Pharmaceutical Advertising Advisory Board (PAAB) — an arm's-length, self-regulating industry body — to alert doctors to the new indication. Members of the Asthma Committee of the Canadian Thoracic Society, after reviewing the promotional material and finding that it indicated the use of Advair as *initial* maintenance therapy for asthma, sent *CMAJ* the commentary that we are publishing here. In this paper, they point out that this use of Advair is not based on clinical trial data and remind readers of proper therapy for new-onset asthma as published in the current guidelines (*Canadian Asthma Consensus Report, 1999* [available at www.cmaj.ca]). While the manuscript was under consideration by *CMAJ*, Health Canada asked PAAB to withdraw their approval of the marketing material. GSK has stopped marketing Advair as initial maintenance therapy for asthma. — John Hoey, *CMAJ*

Combination therapy using inhaled corticosteroids (ICS) (fluticasone propionate or budesonide) with long-acting β_2-agonists (LABA) (salmeterol or formoterol) has been shown to be effective in the treatment of patients whose asthma is not optimally controlled with a moderate dose of ICS. Several pivotal studies[1] have clearly demonstrated in adults the superiority of adding LABA to ICS compared with doubling the dose of ICS in terms of improving asthma control. End points included improving day and night peak expiratory flow (PEF), reducing the need for rescue medication, improving the number of days free of symptoms, as well as reducing the asthma exacerbation rate.[2,3]

Advair, which is a combination of fluticasone propionate and salmeterol, and more recently Symbicort, which is a combination of budesonide and formoterol, are increasingly used as *initial maintenance therapy* for asthma. The use of a single inhaler combining ICS and LABA for all asthma patients is potentially attractive because of the convenience of this treatment, as well as its efficacy and the potential for improving compliance. But this should not be done.

Double-blind randomized trials comparing Advair (200 µg daily) with fluticasone (200 µg daily) as initial therapy are currently only available in abstract form.[4–6] These studies were performed in patients with moderate-to-severe asthma (baseline 1-second forced expiratory volume [FEV_1] of 40%–85% of predicted value, mean value of 66%; subjects demonstrated significant reversibility of FEV_1 post salbutamol [averaging 30%], were symptomatic on most days and required a short-acting β_2-agonist for a mean of > 3 puffs per day). These subjects could not be described as having mild asthma.

The change in FEV_1 or PEF post treatment was the primary outcome and the studies were not powered to show differences in exacerbation rates. There was a greater improvement in FEV_1 in the group treated with Advair compared with the fluticasone-treated group. These results were predictable, because the dosages of inhaled steroids were too low to control symptoms in patients with moderate-to-severe asthma and the concomitant administration of LABA was likely to increase the FEV_1 or PEF. Although the use of a combined therapy may be more effective as initial maintenance therapy than ICS alone in patients with moderate-to-severe asthma, the studies presented to support this indication do not currently allow us to draw this conclusion.

The use of combination therapy in treating mild asthma is even more questionable. The OPTIMA study recently reported by O'Byrne and colleagues[7] compared a low dose of budesonide (200 µg daily) with the same low dose of budesonide combined with formoterol in patients with mild asthma that was not currently being treated with inhaled steroids. These subjects were followed for 1 year. The main outcome was the exacerbation rate in the 2 groups. The study showed no difference between the 2 groups after one year of follow-up. There was a predictable

small increase in the FEV_1 (5.87% v. 4.04% of predicted value) and morning PEF (31.8 L/min v. 15.1 L/min) in the group receiving both budesonide and formoterol compared with the subjects receiving budesonide alone, but this difference is unlikely to be clinically significant and does not reflect improved asthma control.

Therefore, in the absence of convincing evidence in the literature showing a clear superiority of combined therapies over ICS alone for the initial treatment of asthma, the Canadian asthma consensus guidelines are still valid in stating that combined therapies should not be used as first-line therapy for asthma.[8] One may argue that there is no harm in prescribing a combined therapy, because it seems at least as effective as ICS alone. However, the wide prescription of combined therapies instead of ICS alone in initial maintenance therapy for asthma would increase the cost of asthma treatment, because for the same dosage of ICS the combined therapies are more than twice as expensive as ICS alone. In a health care system that is already struggling with the increasing cost of medication, it is our responsibility to avoid prescribing expensive drugs without evidence of their superiority over the standard treatment.

Clearly, further studies are needed in which patients with mild asthma are recruited with adequate sample sizes to look at exacerbations as an end point. In the interim, patients on LABA with mild uncontrolled asthma should be treated with a trial of ICS in the first instance. If patients remain symptomatic while using ICS, and issues relating to adherence, inhaler technique, and appropriate education and environmental control measures have been addressed, only then should combination therapy be considered. Physicians should consult the Canadian asthma consensus guidelines for the management of asthma.[8]

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