Critical Appraisal

The GOAL study

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Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels R, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL Study. *Am J Respir Crit Care Med* 2004;170:836-44.

Research question

Is asthma control, as defined by the Global Initiative for Asthma[1] and the National Institutes of Health[2] (**Table 1**), better achieved using an escalating dose of fluticasone propionate alone (F) or using fluticasone in combination with the long-acting beta-2 agonist salmeterol (F/S)?

Type of article and design

One-year, stratified, randomized, double-blind, parallel-group study involving patients recruited from general practice and hospital-based clinics.

Relevance to family physicians

Asthma is one of the most common chronic diseases managed by family physicians. Many guidelines recommend treating asthma patients with inhaled corticosteroids (ICS) combined with long-acting beta-2 agonists.[1-3] Studies have shown that combination therapy is associated with better asthma control than higher doses of ICS alone are.[4,5] This study is unique in that it attempts to determine whether guideline-defined asthma control can be achieved (using F alone or F/S) in patients with varying disease severity, including patients managed in primary care.

Table 1. Well controlled and totally controlled asthma as defined by the Global Initiative for Asthma (GINA) and the National Institutes of Health (NIH)[1,2]

SYMPTOMS	GOALS OF GINA AND THE NIH	TOTALLY CONTROLLED	WELL CONTROLLED
Daytime symptoms	Minimal (ideally none)	Each week, all of: None	Each week, two or more of: ≤ 2 days with symptom score > 1
Rescue beta-2 agonist use	Minimal (ideally none)	None	Use on ≤ 2 days and two occasions or fewer per week
Morning peak expiratory flow	Near normal	≥ 80% of predicted every day	≥ 80% of predicted every day
Nighttime awakening	Minimal (ideally none)	None	All of: None
Exacerbations	Minimal (infrequent)	None	None
Emergency visits	No	None	None
Treatment-related adverse events	Minimal	None enforcing change in asthma therapy	None enforcing change in asthma therapy

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Overview of study and outcomes

This study focused on patients with suboptimally controlled asthma who were stratified based on their use of ICS before the study. Patients in stratum 1 were not taking steroids. Patients in stratum 2 were taking 500 mcg or less of beclomethasone dipropionate or equivalent. Patients in stratum 3 were taking 500 to 1000 mcg or less of beclomethasone dipropionate or equivalent.

The study had two phases. During phase 1 (dose escalation), treatment was stepped up every 12 weeks until either asthma was totally controlled or the highest dose of F alone or S/F had been administered (F—500 mcg twice daily, S/F—50/500 mcg twice daily). Patients were entered into phase 2 after achieving total asthma control or after 12 weeks of taking the maximum dose of either medication. There was no tapering of treatment during phase 2.

A total of 5068 patients from 826 centres in 44 countries were screened; 3421 qualified for inclusion. Phase 1 was completed by 3039 patients; phase 2 was completed by 2890 patients.

Results

Total control was achieved across all strata in 31% and 19% of patients after phase 1 ($P < .001$) and in 40% and 28% of patients at 1 year with S/F and F, respectively. Good control was achieved across all strata in 63% and 50% of patients after phase 1 ($P < .001$) and 71% and 59% of patients at 1 year for S/F and F, respectively. Across all strata, 68% and 76% of patients were receiving the highest dose of S/F and F, respectively, at 1 year.

In each of the three strata, control was achieved more rapidly and at a lower dose with S/F than with F. Twenty-four–hour urinary cortisol levels were measured in only 194 patients; reductions ranged from 23% to 28% in subjects who received the highest dose of medication. Exacerbation rates were significantly lower with S/F than with F alone in each stratum.

Analysis of methodology

In this study, medication doses were stepped up until total control was achieved or until the maximum dose of medication was administered. Limitations of this study include the large number of subjects who did not meet the inclusion criteria (1647 patients, or 32% of the total cohort). Coupled with the fact that only poorly controlled patients were included, this could create a bias that would limit application of these data to many patients encountered in primary care.[4] For example, the finding that asthma was better controlled with S/F in the steroid-naïve group contrasts with findings in the literature regarding steroid-naïve patients with mild asthma.[4] The lack of tapering once asthma control had been achieved does not reflect recommendations in current asthma guidelines.[1-3] Given the focus on total control, the trial design does not permit determination of the minimum dose necessary to control asthma well. Finally, the lack of a control group makes interpretation of continued improvement with sustained treatment difficult.

Application to clinical practice

Results of this study suggest that, even in a well controlled clinical trial, only a few patients achieve total asthma control despite use of high doses of S/F or F alone over a prolonged period. These findings suggest that current guideline recommendations are unrealistic, particularly when we consider that outcomes would be even less impressive in the real world. We do not know whether more patients (with less severe disease) could achieve total control using the strategy employed in the GOAL study.

Most patients taking S/F and F achieved well controlled asthma, but it should be remembered that most patients received the highest dose of medication for between 7 and 10 months. Absence of a tapering strategy is problematic given the possibility of side effects

at high doses of ICS[6] and data that suggest that asthma control could be maintained with lower doses of combination therapy in patients with moderate-to-severe disease.[4]

Bottom line

- Asthma control was achieved more rapidly and with lower doses of ICS when salmeterol was added.
- Despite use of high doses of S/F or F for a prolonged period, only a minority of patients achieved total control.
- Family physicians should not assume a causal relationship between sustained high doses of S/F or F and good asthma control.
- Further studies that include a tapering treatment strategy are required to provide a meaningful therapeutic framework consistent with current guidelines. Such studies should include patients with mild disease in order to evaluate the role of combination medication as initial therapy in steroid-naïve patients.
- While this study describes some interesting concepts, application of the findings in primary care is substantially limited by the trial design, which included questionable use of high doses of ICS for prolonged periods.

Points saillants

- L'ajout de salmétérol a permis de contrôler l'asthme plus rapidement et avec des doses plus faibles de CSI.
- En dépit d'une utilisation de fortes doses de S/F ou de F pendant une période prolongée, une minorité de patients ont réussi à atteindre une maîtrise totale.
- Les médecins de famille ne devraient pas présumer de l'existence d'une relation causale entre de fortes doses soutenues de S/F ou de F et une bonne maîtrise de l'asthme.
- D'autres études plus approfondies, notamment sur une stratégie de traitement décroissant, sont nécessaires pour produire un cadre thérapeutique significatif, conforme aux directives actuelles. De telles études devraient inclure des patients souffrant d'une forme légère de la maladie afin d'évaluer le rôle de la médication combinée comme thérapie initiale chez des patients n'ayant pas déjà pris de corticostéroïdes.
- Si cette étude décrit certains concepts intéressants, l'application de ses constatations dans le milieu de première ligne est considérablement limitée par la conception de l'étude, qui comportait un recours questionnable à de fortes doses de CSI pendant des périodes prolongées.

References

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