

EDITORIAL

Goals of asthma treatment: how high should we go?

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In the textbook "Respiratory Diseases", published in 1981, CROFTON and DOUGLAS [1] commenced the discussion of asthma management with the comment "It must be admitted that the treatment of asthma is largely palliative". The chapter provides a bleak picture of high mortality, frequent symptoms, and disabling side-effects of treatment. The use of inhaled corticosteroids (ICS) and, later, long-acting β_2 -agonists, has produced extraordinary improvements in asthma outcomes, particularly in the burden of disease for patients. More recent attention has focussed on fine-tuning asthma treatment, the aim being to return the patient towards the disease-free state, *i.e.* not just to improve lung function, which has long been the preferred outcome variable for clinical trials, but to improve the whole spectrum of asthma features, summarised in the expression "asthma control".

These concepts have been addressed by BATEMAN *et al.* [2], reporting the results of the Gaining Optimal Asthma control (GOAL) study. The GOAL study [2] arose from scientific and clinical interest in determining the proportion of asthma patients who could achieve a stringent definition of asthma control. The commercial setting within which this question was examined was a double-blind randomised controlled trial comparing salmeterol and fluticasone combination (SFC) and fluticasone propionate (FP), given *b.i.d* by Diskus/Accuhaler for 12 months in patients with suboptimally controlled asthma at entry. The GOAL study [2] has raised several interesting issues relating to optimal asthma management, and the way in which response to treatment should be assessed.

The GOAL study [2] was planned in the late 1990s, when there was considerable interest in the potential impact of high doses of ICS, with or without long-acting β_2 -agonists, in achieving better outcomes in asthma. At the time, international asthma guidelines recommended either a "step-up" or a "start-high, step-down" approach to asthma management, and the former was adopted in the GOAL study. Subjects without complete asthma control after 12 weeks on the lowest dose level (equivalent to $400 \mu\text{g}\cdot\text{day}^{-1}$ beclomethasone dipropionate (BDP)) were stepped up to $1,000 \mu\text{g}\cdot\text{day}^{-1}$ BDP equivalent and then, if necessary, to $2,000 \mu\text{g}\cdot\text{day}^{-1}$ BDP equivalent. After 12 weeks on the highest dose level, or following the achievement of the Totally-Controlled Asthma category, the final dose was maintained to 12 months. Subjects were recruited to one of three strata, depending on ICS use at entry.

The GOAL study [2] was a huge undertaking, with >3,400 participants, meticulous data collection and an impressively high completion rate (85%). As might be expected from previous studies, treatment with SFC resulted in greater improvement than FP alone in individual asthma outcomes,

such as lung function, quality of life and exacerbations. The same pattern was seen for pre-defined composite measures of the Well-Controlled and Totally-Controlled Asthma, which incorporated symptoms, reliever medication use, morning peak expiratory flow, night waking, exacerbations and side-effects of treatment. Most of the benefit was obtained from the ICS component; however, there was a smaller but statistically significant contribution from the additional salmeterol, primarily for subjects who, at entry, were already taking ICS, but with little extra effect in the group who were steroid-free at entry. The effect size for combination therapy was probably favoured by the magnitude of bronchodilator reversibility at entry (22–23%), and the statistical significance favoured by the large sample size, particularly when the three strata were combined for some analyses. By the end of the GOAL study [2], with combination therapy, 71% of subjects achieved Well-Controlled Asthma and 41% achieved Totally-Controlled Asthma. Because treatment was stepped up unless Totally-Controlled Asthma was achieved, the highest dose of $2,000 \mu\text{g}\cdot\text{day}^{-1}$ BDP equivalent was taken by 68% (SFC) and 76% (FP) subjects, for a period of between 7–10 months, but the majority of subjects who achieved Totally-Controlled Asthma did so at the lowest dose. Low rates of exacerbations were seen in all groups, including those whose asthma remained in the category of Uncontrolled.

One of the problems with a large multinational study is the lead time from original concept to publication of results. To some degree, the treatment approach used in the GOAL study [2] highlights the extent to which asthma management has changed in the last 5 yrs. There has been increasing recognition that the majority of benefit from ICS is obtained with doses $\sim 400 \mu\text{g}$ BDP equivalent [3, 4], that corticosteroids can be down-titrated in most patients without loss of control [5, 6] and that clinical features cannot distinguish between non-steroid-responsive neutrophilic asthma and steroid-responsive eosinophilic asthma [7]. Furthermore, a treatment algorithm in which corticosteroid dose was determined by sputum eosinophils resulted in better outcomes than did a clinical algorithm based on symptoms and lung function [8]. Coupled with, and to some extent driving these developments has been increasing awareness of the potential long-term systemic risks of high dose ICS [9] and of the steep dose-response for local side-effects [10].

Current asthma guidelines still offer either a step-up or start-high approach to initiation of treatment, but there is now a strong recommendation to find the minimum effective dose with both of these strategies. BATEMAN *et al.* [2] suggest that additional benefit may be derived from sustaining regular treatment for up to 6–9 months, based on the observation of continuing improvement during the maintenance phase of the GOAL study. As the authors of the GOAL study [2] acknowledge, the lack of a relevant control group means that this hypothesis cannot be tested from the study results. Other studies have demonstrated progressive improvements in airway hyperresponsiveness [11, 12] and structural changes

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[12] with continued corticosteroid treatment. However, an 18-month study from the institute of the present author showed continuing improvement in individual and composite measures of asthma control and in airway hyperresponsiveness during progressive reduction of budesonide dose which commenced after only 4 months of treatment [13], indicating that maintenance of high ICS doses is not essential to long-term improvement in asthma.

The composite measures of Well-Controlled and Totally-Controlled Asthma have not been used previously as treatment determinants or as study endpoints. They were derived from the Global Initiative for Asthma aims of asthma treatment [14]. By definition, fewer patients will satisfy a composite categorical criterion than will satisfy any one of the components individually. In asthma, although a single measure may over-estimate control, a composite categorisation may underestimate control because of lack of specificity of most of the clinical features of asthma, manifest by overlap with concurrent conditions. For example, cough due to concurrent post-nasal drip, or breathlessness on exertion due to lack of fitness, may determine categorisation as Uncontrolled asthma, but would not respond to increased ICS. Whilst appropriate for answering the GOAL study question [2], the categories of Well-Controlled and Totally-Controlled Asthma have limited utility for assessment of asthma control in clinical practice as they both lie at the extreme of the range of asthma control. For example, if in one 8-week assessment a subject woke every night because of asthma and used reliever medication many times per day, but in the next 8 weeks experienced only 6 days of mild symptoms requiring reliever medication, asthma would be categorised as "Uncontrolled" in both periods. The inclusion of exacerbations in the composite measure of asthma control raises some interesting issues. When the GOAL study was planned, it was believed that any asthma exacerbation represented a failure of asthma control, and this led to the long assessment period (8 weeks) at each dose step. Whilst overall exacerbation rates are undoubtedly reduced by corticosteroid and combination therapy [15], it has now been demonstrated that viral exacerbations can occur during good control [16], that their features differ from poor asthma control [16], and that in experimental studies they are not prevented by ICS treatment [17]. However, many outcome measures, including the composite categorisation used in the GOAL study [2], cannot distinguish between viral exacerbations and poor asthma control.

Any discussion about asthma management must be tempered by awareness of patient attitudes. Patient weighting of the importance of individual asthma symptoms [18] appears to differ from that of clinicians [19]. In addition, patients have powerful lay beliefs relating to asthma medications. BOULET [20] found that the majority of users and nonusers of ICS described fears about side-effects, particularly anabolic effects. Also, patients commonly feared that asthma medications would lose their effectiveness if taken long-term and that doses would need to be progressively stepped up in order to maintain their effect [20]. It is worth noting that the treatment algorithm used in the GOAL study [2] has the potential to re-inforce these lay beliefs. Patients deal with such fears by using lower doses than those prescribed or by taking medication "holidays", in order to maintain effectiveness for when it is needed. Such attitudes may contribute to the disparity between what can be achieved in a clinical trial environment, such as in the GOAL study [2], and what is currently being achieved in the community [21].

The observed risks of ICS treatment, of course, are minor compared with the risks of untreated asthma and with the side-effects of oral corticosteroid treatment which were clinically obvious in the 1960–1970s, but this does not

remove the need to minimise current exposure. There is increasing awareness of the potential for high-dose ICS to contribute to osteoporosis, cataract and glaucoma, but these, like local side-effects, are unlikely to be identified by adverse event reporting in clinical trials. In this context, the striking reductions in urinary cortisol in the GOAL study [2] (23–28% in subjects who received the highest dose), warrant more concern than they have perhaps received in the paper, as ICS are normally given for much longer than 12 months, and changes in indirect markers may flag the potential for other longer-term side-effects.

What is the likely impact of publication of the GOAL study [2] results on asthma management practices? The study has shown that Well-Controlled Asthma can be achieved in nearly three-quarters of subjects, in marked contrast with the levels of control observed in community studies [21]. This is an important message and should change the expectations of both clinicians and patients. However, there is an urgent need for clinical tools to identify noneosinophilic asthma or other non-steroid-responsive conditions, in order to avoid over-treatment. The GOAL study [2] will provide a valuable resource for prospective clinical identification of patients whose asthma remains "Uncontrolled" despite maximal doses of ICS or combination therapy (22–53% of subjects in the GOAL study), which may help to tailor treatment in the future. The results are unlikely to change current cost-benefit recommendations about first-line treatment, because of the small effect size for combination therapy in the steroid-free group; even in those previously on treatment, most of the benefit was gained from the ICS component. However, the treatment algorithm which was used resulted in very high doses of ICS, even in subjects receiving combination therapy, and it is important that it is not assumed that a causal relationship between sustained high doses and good control has been demonstrated. Care will need to be taken in the promotion of the GOAL study [2] results, in order to avoid perpetuation of this assumption, as this could readily result in confusion at the primary care level about current guidelines for minimising corticosteroid doses. The main concern for clinical practice is that use of an algorithm which steps up and sustains treatment if total control is not achieved could delay the search for contributory factors, such as cigarette smoking, concurrent medical conditions and poor adherence.

The Gaining Optimal Asthma controlL study provides important information about ideal asthma outcomes, although there may be other ways to achieve these goals. One of the residual questions from the study is not only whether maximal doses of combination therapy should be used for long periods in an attempt to achieve complete control of all features of asthma, but also whether patients would value the potential incremental benefit sufficiently to concur with such a treatment approach.

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