EDITORIAL

Increasing the dose of inhaled corticosteroid when asthma deteriorates – does it prevent severe exacerbations?

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One of the key goals of asthma management is the prevention of exacerbations, but despite the striking reductions in exacerbation rates that are seen with inhaled corticosteroid (ICS)-containing medications,[1] exacerbations are not completely eliminated even when asthma is clinically well-controlled. As a result, clinical practice guidelines emphasize the need for all patients to be given a written asthma action plan, so they will know what to do in response to worsening asthma in order to prevent further deterioration and avert the need for systemic corticosteroids or urgent healthcare utilization.

Despite the strength of the evidence for the benefit of action plans as part of self-management education,[2] clinical practice guidelines contain little advice about the specific therapeutic strategies that an action plan could/should contain.[3] In fact, the therapeutic options for action plans narrowed several years ago, following the publication of 3 double-blind randomized controlled trials,[4-6] which showed that when asthma began to worsen, the previously recommended strategy of doubling the dose of maintenance ICS was not effective. As a result, for patients prescribed fixed dose maintenance ICS or ICS/long-acting β_2-agonist (LABA), current international guidelines largely limit their therapeutic recommendations for worsening asthma to increasing reliever medication, followed by commencement of oral corticosteroids if symptoms worsen or fail to improve.[7,8]

This approach, in which oral corticosteroids form the second step of the action plan, is not necessarily suited to all patients. Short courses of oral corticosteroids have side effects such as mood disturbance, insomnia, and appetite changes, which are well-recognized by patients and may be severe in their clinical manifestations.[9] However, these adverse effects are often not recognized in clinical trial reports, unless specific questionnaires are used.[10] In the study by Rice-McDonald et al.,[6] 67% of patients receiving rescue prednisolone treatment reported mood changes and 64% reported insomnia. Up to a third of patients may delay in seeking medical care for worsening asthma because of fear that they will be given systemic corticosteroids.[11] Oral corticosteroids may also trigger diabetic instability or cardiac failure in patients with underlying medical problems. Apart from these short-term side effects, repeated short courses of oral corticosteroids (≥2.5 courses/year) significantly increase the risk of osteoporosis in adults,[12] and in a prospective study in children, reduced bone density in adolescence was seen with even lower exposure (≥5 courses over 7 years).[13] Self-administration of oral corticosteroids should thus not be perceived as a benign strategy, and there has been interest in exploring alternative strategies for worsening asthma that may have better effectiveness and/or lower risk of side effects.

While doubling of ICS has not been shown to prevent severe exacerbations, Oborne et al.[14] have now provided evidence from a well-designed randomized double-blind study to support an alternative approach to worsening asthma, namely a quadrupling of ICS dose for 7 to 14 days. The investigators deliberately used a pragmatic design so that the results would be generalizable to self-management in clinical practice. For this reason, the inclusion criteria for the study were broad, with patients eligible with any ICS (± LABA) and any device, and with current smokers not excluded. Baseline characteristics of the 403 study participants indicated that they had mild to moderate asthma, with mean forced expiratory volume in 1 second of 83% predicted and mean ICS dose 500 mcg/day; around 40% were using ICS/LABA at entry. The quadrupling of each

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patient's maintenance ICS dose was achieved by the addition of an extra ICS inhaler, and the control group received a matching placebo inhaler. The trigger for commencing the study inhaler was based on both symptoms and peak expiratory flow (PEF), in that patients were only required to commence recording morning PEF if symptoms worsened or at the onset of a cold. The authors reported that the primary analysis of the whole study population showed a reduced need for oral corticosteroids in the high-dose ICS group, which approached statistical significance, but the interpretation of this intention-to-treat analysis was made difficult by an unexpected and probably chance imbalance in the proportion of intervention and control patients who started the study inhaler. In a planned secondary analysis of patients who started the study inhaler due to worsening asthma, only 21% of those randomized to high-dose ICS required oral corticosteroids compared with 50% of those who received placebo ($P = 0.004$). A further strength of the study, in terms of relevance to clinical practice, was that the majority of these oral corticosteroid courses were commenced on instruction from the patient's general practitioner (i.e., according to conventional clinical indications) rather than according to a protocol-defined criterion.

This study was planned on the basis of accumulating evidence about the potential role of high-dose ICS in preventing or treating exacerbations. Several studies have shown that the majority of spontaneously occurring exacerbations are associated with eosinophilic inflammation,[15-17] and eosinophilic exacerbations are particularly reduced when ICS doses are adjusted by a sputum-guided algorithm.[18] Several randomized controlled trials of high-dose ICS have been carried out in patients presenting to an emergency department (ED) or admitted to the hospital. A meta-analysis of 17 randomized double-blind studies examining rapid effects (≤4 h) of ICS[19] showed that administration of multiple doses of ICS in quick succession increased the odds of early discharge from ED compared with systemic corticosteroids or placebo (odds ratio 4.7 [95% confidence interval 2.97–7.42]), with lesser advantages or no difference when single or widely-spaced doses were used. Dose effects were also seen for admission rates and lung function. For patients discharged from ED or hospital, 3 randomized double-blind studies have shown high-dose ICS to have similar effects to a standard course of oral corticosteroids.[20-22] A potential mechanism for the effects of high-dose ICS in the context of worsening asthma can be seen from studies which demonstrate reduction of sputum eosinophils within a few hours, considerably faster than is achieved with systemic corticosteroids.[17,23] Further insight into the effect of increasing ICS during exacerbations is obtained from studies of the budesonide/formoterol as maintenance and reliever regimen;[24] the reduction in severe exacerbations that is achieved with this approach despite overall relatively low ICS doses suggests that the early increase in ICS/LABA dose may help to abort the inflammatory cascade and sequential bronchoconstriction that are associated with asthma exacerbations.

Few studies have examined high-dose ICS for exacerbations in community-based settings. For patients presenting to general practitioners with worsening asthma, Levy et al. reported a similar rate of treatment failure with high dose fluticasone propionate vs. oral prednisolone,[25] and for asthma clinic patients with at least 5 days of worsening asthma, Di Franco et al. reported similar clinical outcomes but greater improvements in sputum eosinophilia during treatment with high dose fluticasone vs. oral prednisolone.[16] However, no previous studies have examined the early introduction of high-dose ICS, at a stage of worsening asthma when the use of oral corticosteroids would not yet be warranted.

This paucity of evidence may reflect the challenges of designing and conducting intervention studies aimed at preventing asthma exacerbations. One problem lies in attempting to study events that occur infrequently and unpredictably. Like other investigators, Oborne et al. found that exacerbation rates during their study were lower than expected, perhaps due to the "clinical trial effect" by which patients have more contact with health professionals, greater attentiveness to their asthma through monitoring requirements, and potentially better adherence with maintenance medications. Because of the difficulty in capturing spontaneous exacerbations, some investigators have examined the effect of high-dose ICS on exacerbations induced by withdrawal of ICS.[23,26] However, the pathophysiological characteristics of ICS-withdrawal exacerbations, and their response to treatment, may differ from those of spontaneously occurring exacerbations, particularly those triggered by viral infections.[27]

A further major problem with study design lies in the choice of criteria for worsening asthma, since for a prospective study aimed at preventing severe exacerbations, the intervention needs to be delivered at a time when the exacerbation would be considered to be only mild or moderate. The American Thoracic Society/European Respiratory Society Task Force on asthma control and exacerbations[28] highlighted the difficulty of providing standardized definitions for exacerbations of any grade of severity. It is generally accepted that the prescription of oral corticosteroids for 3 or more days implies a clinician assessment that the exacerbation was clinically important; such events are now defined as "severe exacerbations" for the purpose of retrospective analysis of clinical trial data. However, there are no standardized criteria for mild or moderate exacerbations that are sufficiently validated for use in clinical practice or prospective clinical trials.[28] It should be noted that the same uncertainty about selection of criteria for definition of exacerbations in clinical trials also applies in clinical practice to the instructions which should be given to patients in their written asthma

action plan about when to initiate oral corticosteroids. For prospective studies, as in clinical practice, the balance between specificity and sensitivity of exacerbation criteria is crucial – on the one hand, one needs to be confident that the episode is outside the patient's usual day-to-day variation in order to avoid overtreatment, but on the other hand, excessive delay in initiating treatment in order to confirm the occurrence of an exacerbation should be avoided for safety reasons. The criteria for initiation of study medication which were used by Oborne et al. (15% fall in PEF from baseline mean on 2 consecutive days, or 30% fall on 1 day) are similar to those which have been used in previous action plan studies,[29] and are simple to implement in clinical practice.

The above studies of high-dose ICS for the prevention or treatment of exacerbations have provided a new therapeutic option for asthma action plans. Implementation of this strategy in clinical practice could be achieved by the same means as was used in the study by Oborne et al., i.e., by the addition of a high-dose ICS inhaler to the patient's usual maintenance medication of ICS or ICS/LABA, for 7 to 14 days. However, patient-specific factors should be taken into account when considering what advice to give patients. These factors include patient acceptability, cost, and side effects. Compared with high-dose ICS, oral corticosteroids are cheap and have a long shelf-life. Cost is already known to have a substantial impact on adherence with maintenance ICS medications,[30] and many patients may not be able to afford to purchase an extra ICS inhaler during an exacerbation. On the other hand, side effects of the various interventions also need to be taken into account. As previously mentioned, use of oral corticosteroids carries the potential for cumulative long-term risks such as osteoporosis and cataracts, particularly with repeated or inappropriate self-administration. Use of ICS may reduce the potential for corticosteroid side effects, as was seen for cortisol suppression in a comparison of hih-dose ciclesonide and prednisolone in management of asthma exacerbations.[26] For high-dose ICS themselves, side effects such as dysphonia are often not perceived by patients to be health problems, and hence are underreported in clinical trials unless specific questionnaires are used.[6,10] Patients with heavy reliance on their voice, e.g., singers, teachers, may be particularly aware of or susceptible to dysphonia with even short-term high-dose ICS use, so the patient's occupation and previous experience should be taken into account when choosing an action plan strategy.

Asthma guidelines recommend that every patient should have a written asthma action plan. With the work of Oborne et al.,[14] there are now 3 broad models for constructing an action plan, to guide patients in their initial response to worsening asthma:

1 increase reliever as needed

2 increase reliever as needed, and add high-dose ICS for 7 to 14 days

3 for patients using budesonide/formoterol maintenance and reliever therapy, increase budesonide/formoterol as symptoms increase, and decrease it as they resolve.

For each of these initial strategies, oral corticosteroids remain the treatment of choice if symptoms deteriorate or fail to respond. Although there is evidence for lower usage of oral corticosteroids with the second and third options, these approaches will not be suitable for all patients. More research is needed to compare the effectiveness, cost, side effects, and patient acceptability of each of these options, in order to provide clinicians with evidence to support the choice of strategies for managing worsening asthma.

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FROM THE EDITOR

Synopsis: Oborne J, Mortimer K, Hubbard RB, et al. Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. Am J Respir Crit Care Med. 2009; 180: 598-602.

The authors of this randomized study investigated whether quadrupling the dose of inhaled corticosteroid when asthma control started to deteriorate, reduced asthma exacerbations requiring treatment with oral corticosteroids, when compared to patients in whom inhaled corticosteroids were not increased. A total of 403 patients were randomized to take an inhaler that provided a quadrupling (active group) or no change (control group) in inhaled corticosteroid dose when asthma control started to deteriorate. The occurrence of asthma exacerbations was similar in both groups in the analysis of all patients. However, in a preplanned analysis of the 94 patients who actually started the study inhaler (placebo or active drug), the risk of exacerbation was lower in the active group compared with controls (relative risk reduction – 57%). The authors conclude that while the primary endpoint did not differ, quadrupling of inhaled corticosteroid dose may still be a promising treatment option that requires further investigation.