

Editorials

What to do at step 3 of the asthma guidelines—increase the dose of inhaled corticosteroids or add a long-acting β -agonist drug?

Key words: Asthma, guidelines, inhaled corticosteroids, long-acting beta antagonists

Currently, the major unresolved issue in asthma management is the stage at which long-acting β -agonists should be introduced for a patient whose symptoms are not optimally controlled with regular inhaled corticosteroid therapy. This is reflected in the Global Initiative for Asthma (GINA) guidelines, in which it is recommended that a long-acting β -agonist be added in patients with moderately severe asthma receiving between 200 and 1000 $\mu\text{g}/\text{d}$ beclomethasone dipropionate (BDP) or equivalent.¹ This 5-fold range of inhaled corticosteroid dose at which a long-acting β -agonist is added shows the uncertainty that exists in terms of the preferred therapeutic regimen. To resolve this uncertainty, it is necessary to consider three issues: the dose-response relationship of inhaled corticosteroid therapy, the comparative efficacy of adding a long-acting β -agonist drug versus increasing the dose of inhaled corticosteroid therapy, and whether there are any safety concerns regarding the use of long-acting β -agonist therapy, in particular whether its use might mask a worsening of airways inflammation, as has been previously suggested.²

In this edition of the Journal, Wallin et al³ have undertaken a study to test the hypothesis that the addition of the long-acting β -agonist salmeterol to the inhaled corticosteroid fluticasone propionate (FP) at a dose of 400 $\mu\text{g}/\text{d}$ has a significant clinical benefit and does not result in a worsening of bronchial inflammation compared with increasing the dose of FP to 1000 $\mu\text{g}/\text{d}$. In this landmark study the authors have addressed the 3 crucial issues on which the appropriate use of long-acting β -agonist drugs needs to be determined.

In terms of the dose-response relationship of inhaled corticosteroid therapy, this study showed that there was

Abbreviations used

BDP: Beclomethasone dipropionate

FP: Fluticasone propionate

no therapeutic benefit in increasing the dose of FP from 400 to 1000 $\mu\text{g}/\text{d}$. This is consistent with previous studies that have shown that for all clinical outcome measures, including exacerbations, there is minimal if any therapeutic benefit of increasing the dose of FP beyond 500 $\mu\text{g}/\text{d}$.⁴ As quantified in the recent meta-analysis of dose-response studies of FP, 90% of the maximum therapeutic benefit is achieved with doses of around 200 $\mu\text{g}/\text{d}$, and the maximum effect is obtained with a dose of around 500 $\mu\text{g}/\text{d}$.⁴ This indicates that 500 $\mu\text{g}/\text{d}$ FP (or 1000 μg of BDP or budesonide) should be considered a high dose, representing the top of the therapeutic dose-response curve in moderate or severe asthma.

The study by Wallin et al³ also considered whether there is a different dose-response relationship for inhaled corticosteroids in terms of modifying the underlying airways inflammation compared with clinical outcome measures. Although most previous studies have attempted to investigate this issue through measurement of surrogate markers, including inflammatory cells in sputum⁵ or exhaled gases,⁶ these are indirect indices of uncertain relevance. This current study, which investigated the nature and magnitude of airways inflammation through the detailed assessment of bronchial biopsy specimens, found no significant difference in markers of airway inflammation between a dose of 400 $\mu\text{g}/\text{d}$ and 1000 $\mu\text{g}/\text{d}$ FP. This finding is consistent with a similar bronchial biopsy study in which the improvement in lung function and suppression of airways inflammation were optimal at a dose of 500 $\mu\text{g}/\text{d}$ FP with no significant further benefit at 2000 $\mu\text{g}/\text{d}$ FP.⁷ Together, these studies indicate that the dose-response relationship of inhaled corticosteroids is comparable for both airway anti-inflammatory effects and clinical efficacy.

In terms of the second issue, the study showed that the addition of salmeterol led to a significant improvement in lung function compared with increasing the dose of FP. This is consistent with previous studies that have shown that the addition of a long-acting β -agonist drug to inhaled corticosteroid therapy leads to improved asthma control

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compared with increasing the dose of inhaled corticosteroids.^{8,9} However, to date, most but not all of these studies have been limited by using baseline doses of inhaled corticosteroids near or at the top of the dose-response curve. By design, this inevitably leads to a better outcome with the long-acting β -agonist treatment regimen. However, these studies have appropriately formed the basis for the earlier introduction of long-acting β -agonist therapy at a lower dose of inhaled corticosteroid therapy. Currently available evidence suggests that this dosage level is around 200 $\mu\text{g/d}$ of FP (400 $\mu\text{g/d}$ of BDP or budesonide) where 80% to 90% of the therapeutic efficacy has been achieved, with studies having shown a greater efficacy by adding a long-acting β -agonist than increasing the dose of inhaled steroid beyond this level.^{10,11}

In terms of the third issue and the primary outcome of this study, Wallin et al³ have shown that the addition of salmeterol to FP is not associated with any increase in airways inflammation compared with either baseline or higher-dose FP therapy. This finding was based primarily on the measurement of submucosal mast cell and eosinophil numbers in bronchial mucosa biopsy specimens after 12 weeks of treatment, together with measurement of adhesion molecules and cytokines in the biopsy specimens and measurement of markers of inflammation, inflammatory cell activation, and fibroblastic activity in the supernatant of the bronchial wash and bronchoalveolar lavage fluid. These observations extend those of previous studies that have also indicated that salmeterol and formoterol do not result in any worsening of airways inflammation.¹²⁻¹⁴

One related issue that was not addressed in this study is whether the use of long-acting β -agonist therapy outside the strict supervision of a clinical trial might worsen airways inflammation and lead to poor asthma control if it led to a significant reduction in compliance with inhaled corticosteroid therapy. To our knowledge, there have been no studies that have directly investigated this potential problem, despite an initial case report that suggested it was a concern.¹⁵ This represents an important research priority, particularly with the availability of combination inhaled corticosteroid/long-acting β -agonist inhaler devices, which would potentially lead to additional clinical efficacy through improving compliance and guarantee the prescribing physician that the long-acting β -agonist will not be used as a monotherapy.¹⁶

When the findings of the study by Wallin et al³ are taken together with currently available scientific evidence, they provide greater certainty regarding the therapeutic approach to take at step 3 in the asthma guidelines. For patients with unstable asthma, inhaled corticosteroids should be routinely prescribed up to 200 $\mu\text{g/d}$ FP or equivalent in addition to inhaled short-acting β -agonist therapy. Patients whose symptoms are uncontrolled at this stage are likely to obtain greater therapeutic benefit with the introduction of a long-acting β -agonist than further increasing the dose of FP. If the patient's symp-

toms remain poorly controlled with the combination of a long-acting β -agonist and 200 $\mu\text{g/d}$ FP, then an appropriate next step would then be to increase the dose of FP to 500 $\mu\text{g/d}$ together with a long-acting β -agonist, preferably in a combination inhaler device.

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