

Combination inhaled corticosteroid and long-acting β_2 -agonist use and severe asthma exacerbations

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Over the last decade, the aims of asthma management have altered to focus on achieving and maintaining good asthma control and reducing future risks, such as decrease in lung function, asthma exacerbations, hospitalizations, death, and adverse effects from treatment.^{1,2} The benefits of good asthma control include a variety of asthma outcomes that are important to both patients and society. These include no restriction in lifestyle, better physical fitness and quality of life, reductions in patients' perception of the asthma burden, health care resource use, and lower risk of exacerbations, hospitalizations, and death.^{3,4}

Inhaled corticosteroids (ICSs) or combination therapy with an ICS and a long-acting β_2 -agonist (LABA) have become established as cornerstones in guideline-recommended asthma treatment because these therapies have been the most successful in achieving asthma control and reducing future risks in the vast majority of patients with asthma.^{1,2} Changes in the goals of asthma management, as well as treatment recommendations, have revolutionized management from both the patient's perspective and a societal perspective. The main question that remains is whether the clinical benefits balance or outweigh the risks of the treatments?

When regular ICS treatment was introduced 4 decades ago, safety concerns were common, and initially, the treatment was reserved for patients with severe disease. The concerns were based on fears generated by the side effects of oral corticosteroids rather than data generated by using ICSs, but with increasing knowledge and experience, the concerns decreased, and ICSs became a first-line therapy for asthma because the benefits of the treatment clearly outweighed the risks.

The situation is somewhat different for regular therapy with LABAs. This treatment has been used for more than 20 years, and marked clinical benefits on asthma control have been

demonstrated in many controlled studies. Yet concerns persist about their safety, and arguments have been made for restrictions of their use in asthma management.^{5,6} The safety concerns were caused by the findings of an increased risk of asthma-related hospitalizations and deaths in a large phase IV safety study⁷ and a subsequent meta-analysis.^{7,8} The concerns are quite similar to the concerns raised about the use of short-acting inhaled β_2 -agonists (SABAs) in the early 1980s.⁹ At that time, the issue was eventually resolved by means of thorough analysis of data from clinical trials. The studies demonstrated that frequent use of SABAs in patients not receiving regular ICS treatment increased the risk of serious adverse asthma outcomes, such as hospitalizations and death. However, similar risks were not seen in patients using SABAs as rescue treatment together with regular ICS treatment, and it was concluded that the main reason for the serious adverse asthma outcomes seen with frequent SABA use was undertreatment with ICSs rather than direct toxicity of the drugs. Although it is agreed that LABA use as monotherapy in asthmatic patients must also be avoided for the same reasons, there is still a passionate debate about whether the serious risks persist in patients in whom LABAs are added to regular ICS treatment.

A main reason for this is that at present no prospective clinical trials have been conducted to evaluate the effects of ICSs in mitigating the risk of the serious asthma outcomes reported in patients receiving LABA monotherapy. Therefore several attempts have been made to answer this question through additional analyses of the already existing data. However, meta-analyses of LABA safety data, based on efficacy studies, are often confounded by differing ICS doses in the LABA and non-LABA treatment arms. Also, different meta-analyses have specified their own criteria for inclusion or exclusion of studies to be evaluated. Adherence to therapy has not been assessed in many trials, and often no distinction has been made between patients receiving the LABAs and ICSs in separate inhalers or in a single inhaler device. Therefore it is not surprising that there has been some discordance in the findings in various analyses.¹⁰ Finally, the reassuring results from meta-analyses based on randomized efficacy trials have been criticized for not reflecting the real-world clinical environment.⁶

In this issue of the *Journal of Allergy and Clinical Immunology*, Wells et al¹¹ add to the paucity of real-world data by reporting the findings from a large, population-based, real-world observational study comparing the effects of ICSs and fixed-dose ICS/LABA combination therapy on severe asthma exacerbations in a racially diverse population of 1828 patients with a total of 3791 person years of follow-up. Data were obtained longitudinally from a managed care organization, and LABA exposure was estimated from pharmacy data. It was found that ICS/LABA combination therapy had an overall protective effect on asthma exacerbations that was as good as or better than that for ICSs alone. The

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protective effects of ICS/LABA combination therapy seemed particularly marked in patients older than 18 years, male subjects, patients with moderate and severe asthma at baseline, and reassuringly, African Americans (who have been suggested to be at greater risk). Unlike earlier observational studies, Wells et al¹¹ only included patients using a fixed-dose ICS/LABA combination. Furthermore, they accounted for adherence and changing levels of medication use over time.

Although the study is well executed, carefully analyzed, and uses sound methodology, it was not of a sufficient size to make any firm conclusions about severe but rare asthma-related events, such as intubations, death, or both. Yet it is an important contribution to the literature on the perceived risk of serious adverse effects of LABAs. It is reassuring that the results from a carefully executed observational study, mimicking real-world study conditions, are in such good agreement with the findings in the randomized, controlled efficacy trials comparing ICS use alone with a fixed LABA/ICS combination.^{10,12,13} In addition to significant improvements in asthma control, such studies consistently report reductions in asthma exacerbations, need for oral steroid bursts, and asthma-related emergency department visits compared with ICS treatment alone. Because such events normally precede more serious outcomes, such as intubations, death, or both, these findings make it unlikely (but do not prove) that treatment with fixed LABA/ICS combinations *per se* should be associated with an increased risk of these serious outcomes.

The US Food and Drug Administration has requested a series of very large postmarketing clinical trials to evaluate LABA/ICS combination safety,¹⁴ but the most serious asthma outcomes are so rare that even these studies might not be able to provide a definite conclusion. Moreover, the results from these studies will not be available until 2017 at the earliest. What should clinicians do in the meantime?

It would be a disservice to our patients if we, in the fear of doing harm to our patients, waited for the perfect. The study by Wells et al¹¹ supports that a better option would be to follow the recommendations of the asthma guidelines,^{1,2} which unanimously have taken the stand that there is no convincing evidence that LABA/ICS combinations administered in a single inhaler are associated with serious adverse effects. Their benefits on asthma control and

reduction of asthma exacerbations outweigh their risk, and we should be careful not to let the perfect become the enemy of the good.

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