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Can we use the combination formoterol-budesonide in teenagers with moderate or severe asthma?

De Lucas García N[1], Gimeno Díaz de Atauri A[2]
[1]SAMUR-Protección Civil. Madrid. Spain.
[2]Servicio de Pediatría. Hospital Universitario 12 de Octubre. Madrid. Spain.

Correspondence: Nieves de Lucas García, delucasn@gmail.com

English key words: asthma, budesonide, budesonide formoterol drug combination, drug related side effects and adverse reactions.
Palabras clave en español: asma, budesonida, combinación de budesonida y fumarato de formoterol, efectos adversos, reacciones adversas.

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Can we use the combination formoterol-budesonide in teenagers with moderate or severe asthma?

De Lucas García N[1], Gimeno Díaz de Atauri A[2]
[1]*SAMUR-Protección Civil. Madrid. Spain.*
[2]*Servicio de Pediatría. Hospital Universitario 12 de Octubre. Madrid. Spain.*

Correspondence: Nieves de Lucas García, delucasn@gmail.com

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Abstract

Authors´ conclusions: among adolescents and adults with predominantly moderate-to-severe asthma, treatment with budesonide-formoterol was associated with a lower risk of asthma exacerbations than budesonide and a similar risk of serious asthma-related events.

Reviewers´ commentary: although safety doubts about the combination of formoterol and budesonide are not completely clarified, it seems to be safe and effective in the management of moderate or severe asthma in patients over 12 years of age without life-threatening episodes. Doubts remain about children under 12 years of age. In order to definitively recommend its use, independent studies of safety, efficacy and cost-effectiveness comparing it with budesonide alone would be required.

Key words: asthma, budesonide, budesonide formoterol drug combination, drug related side effects and adverse reactions.

¿Podemos utilizar la combinación formoterol-budesonida en adolescentes con asma moderado o grave?

Resumen

Conclusiones de los autores del estudio: en pacientes mayores de 12 años con asma moderada o grave se observó un menor riesgo de exacerbaciones en los tratados con formoterol/budesonida con respecto a los tratados con budesonida sola, con un riesgo similar de efectos adversos graves.

Comentario de los revisores: aunque no se despejan completamente las dudas sobre la seguridad de la combinación de formoterol y budesonida, parece segura y eficaz en el control del asma moderado o grave, en pacientes mayores de 12 años sin episodios de riesgo vital. Se mantiene la duda sobre los niños menores de 12 años. Para poder recomendar definitivamente su uso se necesitarían estudios independientes de seguridad, eficacia y coste-efectividad comparándola con la budesonida aislada.

Palabras clave: asma, budesonida, combinación de budesonida y fumarato de formoterol, efectos adversos, reacciones adversas.

STRUCTURED ABSTRACT

Objective: to evaluate whether addition of formoterol to treatment with budesonide in patients with asthma is associated with an increased risk of asthma-related serious adverse events (SAEs) and whether it improves asthma control.

Design: double-blind randomised control trial (RCT). The protocol was developed in discussion with the Food and Drug Administration (FDA) of the United States.

Setting: 534 centres in 25 countries in Europe, Africa, Asia and America.

Study sample: patients aged more than 12 years with a clinical diagnosis of asthma and at least one exacerbation in the previous year (but none in the previous month). Patients were eligible if they were being treated with an inhaled glucocorticoid (IG) alone or combined with a long-acting β-agonist, or their disease severity or level of asthma control warranted such treatment. Exclusion criteria: history of life-threatening asthma, more than four exacerbations or two asthma-related

hospitalizations in the previous year, poor symptom control in the seven days preceding randomization, or smoking history of more than 10 pack-years. A total of 11 693 patients underwent randomization, of who 11 551 completed the study, but all were included in the intention-to-treat analysis.

Treatment based on severity and level of control: patients were stratified to a dose level of budesonide (80 or 160 µg every 12 hours). Patients were randomly assigned in a 1:1 ratio within their stratum to receive formoterol (4.5 µg) administered through the same inhaler as budesonide (treatment group [TG]) or budesonide alone (control group [CG]) for a period of 26 weeks. Adherence was assessed by means of the dose-actuation counter on each inhaler. The followup consisted of three in-person clinical visits (at 4, 12 and 26 weeks) and monthly telephone calls.

Study endpoints: the primary endpoint was the risk of asthma-related SAE (death, intubation or hospitalization) and the time to the first such event. Other safety assessments: death from any cause, discontinuations resulting from adverse events, and discontinuations resulting from exacerbations. The secondary objective of the study was to evaluate efficacy based on the time to the first exacerbation requiring treatment with glucocorticoids for at least three days, inpatient hospitalization or prescription of glucocorticoids by an emergency department. Secondary efficacy variables: assessment of current asthma control based on the Asthma Control Questionnaire (ACQ-6) and data from patient diaries (use of rescue medication and frequency of symptoms). The primary endpoint was assessed using a two-sided test in which noninferiority was concluded if the upper limit of the 95% confidence interval (95 CI) for the hazard ratio was less than 2.0. Safety data were collected at the end of the study or up to seven days after the last dose. Data on efficacy variables were collected up to seven days after the last dose and assessed in patients stratified by level of control at study entry and by IG dose level.

Main results: the two groups had similar baseline characteristics: at study entry, 9.9% were not using IGs and 40.9% had uncontrolled asthma. Approximately 80% of all patients had 80% or more adherence to the regimen. Asthma-related SAEs occurred in 43 patients in the TG and 40 patients in the CG, and two of the SAEs were asthma-related deaths, both in the TG. Statistical noninferiority was demonstrated for the time to first serious asthma-related event: hazard ratio (HR), 1.07 (95 CI, 0.7-1.65), with similar results in the GI low-dose and high-dose subgroups. As for efficacy, the study found a lower risk of exacerbation in the TG (HR, 0.84; 95 CI, 0.74-0.94) with improved asthma control based on patient diaries and the ACQ-6.

Conclusion: among patients aged more than 12 years with moderate to severe asthma, treatment with budesonide-formoterol was associated with a lower risk of exacerbations compared to treatment with budesonide alone, with a similar risk of asthma-related SAEs.

Conflicts of interest: most authors have received funding from AstraZeneca and other pharmaceutical companies.

Funding source: AstraZeneca.

COMMENTARY

Justification: in 2010, the Food and Drug Administration (FDA) of the United States announced that long-acting β-agonists (LABAs) should not be used alone in the treatment of asthma because there was evidence of their association with an increased risk of asthma exacerbation, hospitalization and death in adults as well as children[1] Later, in 2011, the FDA requested that manufacturers of these drugs carry out clinical trials to assess the safety of LABAs used in combination with corticosteroids compared to the use of corticosteroids alone.[2] The study that we review here and one other published in the same journal[3] were conducted for this purpose.

Validity: the authors concluded by prioritising the secondary objective (efficacy), which was the least protected by the study design and whose results were likely to be less valid. It is possible that acute asthma was insufficiently treated in some cases (unavailability of bronchodilators after using up the provided rescue inhaler) so that LABAs provided an advantage to the treatment group. The upper limit of the confidence interval used to assess efficacy was very close to 1. The authors did not use the gold standard for the assessment of adherence (electronic device) and the method used (dose-actuation counter in the device) could overestimate adherence if patients were to activate the device and then not inhale the medication. The study was a double blind, but did not seem to be a triple blind, and the first draft of the manuscript and the statistical analysis were done by the laboratory that markets the drug. The six-month followup may not have been long enough to avoid biases related to the omission of specific seasons of the year. Outcomes were analysed by intention to treat. The primary endpoint was a composite that combined less-serious events (short-term asthma-related hospitalizations) with asthma-related death, a limitation that could have been easily avoided considering the low expected frequency of asthma-related deaths. The results in adolescents were not analysed separately, although the article did note that the two asthma-related deaths occurred in adults treated with corticoid-formoterol.

Clinical relevance: the study suggests that the combination of formoterol and budesonide can be used for the management of moderate to severe asthma (without life-threatening episodes) in patients aged more than 12 years, with no added risks compared to treatment with budesonide alone. Doubts remain about its use in children aged less than 12 years. If the results were taken as valid, the cost of the medication used in the management of asthma would increase due to the addition of formoterol. Subsequent cost reductions due to decreased hospitalization and fewer days of work missed, as well

as the ultimate benefit of improved quality of life, remain to be studied.

Applicability to clinical practice: the study provides no evidence that would support changes in the management of asthma in children aged less than 12 years. For children aged more than 12 years, the combined use of formoterol and budesonide for asthma control appears to be safe, but the evidence does not support recommending its routine use, which would require independent studies of safety, efficacy and cost-effectiveness comparing it with budesonide alone.

Conflicts of interest: the authors of this commentary have no conflicts of interest to declare.

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