Editorial

Beclomethasone revisited: the modern view of a classic inhaled corticosteroid

Petros Bakakos,
Stelios Loukides,
Konstantinos Kostikas

Editorial Board Pneumon

SUMMARY. Asthma is a worldwide problem affecting more than 300 million people of all ages with a relevant impact on quality of life and healthcare resources. International guidelines recommend the combination of a long acting beta-2-agonist and an inhaled corticosteroid when asthma is not fully controlled by low-dose ICS alone. The beclomethasone/formoterol combination is formulated as a hydrofluoroalkane-134a-containing pressurised metered-dose inhaler, using the Modulite solution formulation technology. Comparative studies of this combination have shown similar efficacy versus budesonide/formoterol and fluticasone/salmeterol in patients with moderate-to-severe asthma. Several studies have indicated that inflammatory and structural changes occur in the small airways of asthmatic subjects. Beclomethasone/formoterol extra-fine formulation results in drug delivery to both central and peripheral airways, so that airway inflammation can be treated uniformly throughout the lower respiratory tract. The improved delivery of beclomethasone/formoterol extra-fine formulation translates into significant clinical benefits compared to traditional large particle inhaled medications. Despite the fixed combination of beclomethasone/formoterol delivering more drug to the lungs, it results in a lower systemic exposure. The beclomethasone/formoterol extra-fine formulation is an advantageous and safe treatment choice for patients with asthma and/or COPD. ***Pneumon 2014, 27(2):125-130.***

Corespondence:
Petros Bakakos, Assistante Professor,
1st Depattment of Respiratory Medicine,
Medical School of National and Kapodistrian University of Athens, "Sotiria" Hospial of Chest Diseases,
Athens, Greece,
11 Konons Str., 116 34 Athens, Greece
e-mail: petros44@hotmail.com

INTRODUCTION

Asthma represents a major global public health issue affecting more than 300 million people of all ages with a relevant impact on healthcare resources.[1] It is characterized by variable airflow obstruction, bronchial hyperresponsiveness, and airway inflammation and various cells and cell products have been implicated in the pathogenesis of the disease.[2]

Inhaled corticosteroids (ICSs) are currently the most effective anti-inflammatory treatment of asthma.[2] However, international guidelines rec-

ommend the combination of a long acting beta-2-agonist (LABA) and an inhaled corticosteroid (ICS) when asthma is not fully controlled by low-dose ICS alone[2]. ICS/LABA fixed-dose combinations have been increasingly used in asthma because they are more convenient for patients[3].

Three preparations are commercially available: fluticasone propionate with salmeterol, budesonide with formoterol and beclomethasone dipropionate with formoterol. The latter is formulated as a hydrofluoroalkane-134a (HFA-134a)-containing pressurised metered-dose inhaler (pMDI), using the Modulite solution formulation technology[4,5]. It delivers extra-fine particles of 100 µg beclomethasone dipropionate and 6 µg formoterol per actuation[5].

Comparative studies of the beclomethasone dipropionate/formoterol combination have shown similar efficacy in terms of improvement in pulmonary function and asthma control versus budesonide/formoterol and fluticasone/salmeterol in patients with moderate-to-severe asthma.[6,7]

THE ROLE OF SMALL AIRWAYS AS THERAPEUTIC TARGET

Small airways are defined as airways of less than 2 mm internal diameter without cartilage.[8,9] Due to the extensive branching pattern of the tracheobronchial tree, the total volume and the surface area of the small airways are much greater that the surface area of the large airways.[8]

The possible involvement of small airway inflammation in the pathophysiology and clinical manifestations of asthma has recently been re-emphasized.[10-12] Small airways disease has not been thoroughly investigated due to difficulties of in vivo sampling and lack of specificity of physiologic measurements for this site of the lung.

However, several studies have indicated that inflammatory and structural changes apart from the large airways also occur in the small airways of asthmatic subjects.[10,13,14] Increased numbers of lymphocytes and eosinophils, uniformly distributed throughout the large and small airways of both mild and severe asthmatics have been demonstrated in autopsy studies from fatal and non-fatal cases of asthma.[10,14] Furthermore, a greater number of activated eosinophils were seen in small compared to large airways, indicating a more severe inflammatory process in the peripheral airways.[15] Additionally, in COPD the peripheral airways are the main site of obstruction.[16]

The small airways are traditionally considered as pathways of small resistance, contributing less than 10% of the total airflow resistance in the lung.[16-18] Accordingly, an extensive damage of small airways may occur prior to the development of any symptoms and before any of the conventional lung function tests become abnormal. The therapeutic challenge is to reverse the damage or prevent its progression to a stage when it becomes irreversible. The main question is whether the currently available anti-inflammatory therapies target the small airways and whether such targeting is important for the optimal clinical response.

FINE PARTICLE BECLOMETHASONE

Following the development of ozone-friendly chlorofluorocarbon (CFC)-free inhalers, pMDI solutions using HFA as a non-CFC propellant have been developed using a new "Modulite" technology.[19] The Modulite platform has been used to develop formulations with extra-fine particles with a mass median aerodynamic diameter around 1.1 mm, suitable for high lung deposition and homogeneous distribution throughout the lung and was originally applied to the development of beclometasone dipropionate [BDP].[19]

Moreover, it was shown that a dose of 100 mg of BDP in the extra-fine formulation delivers a fine particle dose comparable to a 250 mg dose of BDP via a CFC-containing pMDI (ratio of 1:2.5).[5] Another extra-fine formulation of BDP HFA (Qvar) has demonstrated high lung deposition and less cortisol suppression than CFC formulations of BDP.[20] Moreover, HFA-beclomethasone was superior to fluticasone in improvement in airway closure, measured by single-breath nitrogen washout, indicating a greater effect in small airways.[21] A study performing HRCT comparisons between fine-particle HFA-beclomethasone and larger particle aerosol treatment demonstrated less regional gas trapping with the fine-particle aerosol.[22]

Since extra-fine formulations result in drug delivery to both central and peripheral airways, airway inflammation could be treated uniformly throughout the lower respiratory tract. In adults with moderate asthma, BDP extra-fine HFA pMDI was clinically equivalent, in terms of peak expiratory flow rate, to BDP via a CFC-containing pMDI at a dose ratio of 1:2.5.[23,24]

In a recent real-life study, patients who received step-up therapy with fine-particle HFA-beclomethasone were more likely to achieve asthma control compared to those treated with CFC-beclomethasone.[25]

A 12- month randomized trial that evaluated quality

of life in patients with asthma who switched from large-particle BDP to extrafine BDP revealed clinically important improvements in asthma-specific quality of life for the extrafine treated group versus patients treated with large-particle BDP. Such improvements detected in the patient's quality of life but not captured by conventional pulmonary function testing may be attributed to an effect in the small airways with the extrafine formulation.[26]

EXTRA-FINE COMBINATION OF BECLOMETHASONE – FORMOTEROL

For extrafine formulations of ICS/LABA, the risk that higher lung deposition and peripheral distribution might lead to higher systemic exposure is reasonable. In this regard, a recently published pharmacokinetics study compared the systemic exposure of extrafine BDP-formoterol, with an equipotent regimen of BDP nonextrafine plus formoterol extrafine given via separate inhalers.[27] Regarding formoterol (F), the study revealed comparable systemic exposure after the two treatments. However, the 24-h systemic exposure of the active metabolite beclometasone 17-monopropionate (17-BMP - the main metabolite of BDP) was 35% lower with the BDP-F extrafine fixed combination than with the combination, where BDP was non-extrafine. Accordingly, these data indicate that, despite the fixed combination of BDP-F delivering more drug to the lungs, it results in a lower systemic exposure when compared with an equipotent regimen of non-extrafine BDP plus formoterol.[27]

Another study in which the BDP-F combination HFA formulation was labeled with 99mTechnetium (99mTc) showed that a large amount of the inhaled combination was deposited into the lungs (31–34%), with a low variability between healthy subjects, asthmatic, and COPD patients, thus confirming efficient lung delivery regardless of pathophysiological condition. At least one-third of the drug was deposited in the peripheral airways of all three groups of subjects, indicating that the increased airway obstruction in patients had a moderate impact on the pattern of deposition.[28]

In a recent 12-week study, treatment with HFA-BDP/F extra-fine combination, resulted in a trend toward improvement of single breath nitrogen washout closing capacity, providing evidence for efficacy of fine particle combinations in small airways.[29]

The improved delivery of BDP/F extra-fine formulation has the potential to target inflammation and bronchoconstriction in the entire bronchial tree, including the smaller airways which is an anatomical site particularly involved in the progression of asthma and COPD. But does this potential translate into additional clinical benefits?

In a large randomized controlled trial comparing BDP/F fixed combination with the same two drugs administered in large-particle formulations, a comparable improvement in morning PEF but better asthma control was detected in the BDP/F fixed combination group and was considered to be related to the lung deposition profile of BDP/F extrafine formulation.[30]

A large amount of data indicates that smoking is associated with an increased risk of poor asthma control and an impaired corticosteroid response.[31,32]

It has also been demonstrated that tobacco smoke-drug particle interactions, are less likely to affect the drug distribution within the lungs in the case of extrafine formulations, suggesting that especially asthmatic smokers could benefit from extrafine drugs.[33]

The PRISMA study confirmed a higher control level and better quality of life in patients treated with extrafine BDP/F as compared to Budesonide/Formoterol and Fluticasone/Salmeterol at the end of a 12-month observation period. Moreover, the population of this study included a significant proportion of smokers or ex-smokers.[34] The same treatment benefits were observed in former or current smokers compared to non-smoking asthmatics in terms of pulmonary function and GINA asthma control in 619 asthmatics from Belgium.[35]

The fixed combination of BDP and F compared with inhalation of the same dosage of the free combination of the two active treatments in children aged 5–11 years was

Reaching small airways	→	More uniform and thorough bronchodilating and anti-Inflammatory action
Lower systemic exposure	→	More safe, less adverse events
Better improvement in QoL	→	Advanced clinical benefits
Earlier intervention in a "quiet" lung zone	→	Possible changes in the natural history of the disease

FIGURE 1. Beclomethasone/formoterol extra-fine formulation.

not superior in terms of systemic exposure and showed a comparable pharmacodynamic and safety profile.[36]

In patients with severe COPD, the fixed combination of HFA BDP/F given in a total daily dose of 400/24 mg for 48 weeks improved pulmonary function, lessened symptoms and proved to be comparable to budesonide/formoterol (total daily dose 800/24 mg) but at a nominal dose of BDP two-fold lower than the equipotent daily dose of budesonide, and superior to formoterol alone (total daily dose 24 mg).[37] Thus, the BDP/F extrafine combination has the potential to minimise long term corticosteroid related side effects in COPD patients, as the corticosteroid dose used is lower than other fixed-dose ICS /LABA combinations.

A 6-month therapy with extrafine BDP/F resulted in significant improvements in pre-bronchodilation imaging parameters, gained by converting patient-specific high-resolution computed tomography (HRCT) images to detailed three-dimensional computer models of the airways, such as small airway volume and computational fluid dynamics based resistance. Notably, a significant correlation was observed between changes in small airway volume and changes in asthma control score, suggesting that treating the small airways with extrafine BDP/F translates into clinical benefits for patients.[38]

BDP/F combination has a fast onset of action, similar to that of salbutamol, and may represent a good alternative as rescue medication in asthmatic patients.[39]

Moreover, the extrafine BDP/F combination was more effective in reducing asthma exacerbations when given as both maintenance and reliever treatment than when given only as maintenance with salbutamol as needed to asthmatic patients not fully controlled.[40]

An interesting study included asthmatic subjects who changed treatment to BDP/F from other ICS/LABA combination preparations. In this study FVC was the parameter chosen to reflect small airways improvement because it is highly reproducible and readily available in routine practice spirometry.[41,42] After 8 weeks of treatment, the asthmatic subjects with the highest improvement in their % FVC demonstrated also significant decrease in some indicators of airway/systemic inflammation, reflected in CRP, blood eosinophils and exhaled breath temperature, supporting an effect at the level of the small airways through a reduction of air trapping.[43]

The use of aerochambers optimizes the lung delivery of beclometasone and formoterol in subjects that find it difficult to synchronize aerosol actuation with the inspiration of breath and show inadequate inhalation technique. Previous studies with a different combination (i.e. fluticasone/salmeterol) showed a significant increase in total systemic exposure for the ICS administered with the spacer when compared with the pMDI alone.[44] This does not appear to be the case for BDP/F delivered using the Modulite pMDI, since it was shown that the total systemic exposure of beclometasone 17-monopropionate and formoterol was not significantly increased by the use of the AeroChamber Plus spacer.[45]

The evaluation of the inhalation profiles through a new device, the NEXThaler DPI, that delivers fixed dose combination of BDP/F demonstrates that device activation and consistent dose delivery occurs at patient achievable inhalation flow rates, and supports the broad utility of the NEXThaler DPI in patients with asthma.[46]

CONCLUSIONS

Our knowledge on the role of small airways in asthma and COPD is still limited. Even more limited is the data regarding the clinical benefits of targeting small airways with currently available medications. Many of the aforementioned studies are under criticism regarding the selection of patients of interest and sampling techniques and there are certain limitations to the way pathologists, physiologists, radiologists and molecular biologists approach the small airways.

On the other hand, there is no doubt that small airways represent nowadays the area of the lungs where great expectations for future improvements arise. Accumulating recent data add direct or indirect evidence that treating the entire bronchial tree with bronchodilators and inhaled steroids delivered in fine particles with the beclomethasone/formoterol extra-fine formulation provides extra benefits compared to traditional large particle inhaled medications.

What is the exact and long-standing effect of such treatment approach and whether this will have an impact on the natural history of asthma and/or COPD remains to be elucidated. Ongoing research will provide the evidence for or against this argument.

REFERENCES

1. Masoli M et al. The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy 2004; 59: 469-478.
2. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. revised 2009. Available from:

http://www.ginasthma.org.
3. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. Eur Respir J 2007; 29:587-595.
4. Lewis DA, Ganderton D, Meakin BJ, Brambilla G. Modulite: a simple solution to a difficult problem. Respiration 2005; 72(Suppl. 1):3-5.
5. Dhillon S, Keating GM. Beclometasone dipropionate/formoterol: in an HFA-propelled pressurised metered-dose inhaler. Drugs 2006; 66:1475-1483.
6. Papi A, et al. Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma. Allergy 2007;62:1182–1188.
7. Papi A, et al. Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. Eur Respir J 2007; 29:682–689.
8. Weibel ER. Principles and methods for the morphometric study of the lung and other organs. Lab Invest 1963;12:131-155.
9. Ranga V, Kleinerman J. Structure and function of small airways in health and disease. Arch Pathol Lab Med 1978;102:609-617.
10. Hamid Q, Song Y, Kotsimbos TC, et al. Inflammation of small airways in asthma. J Allergy Clin Immunol 1997;100:44-51.
11. Martin RJ. Therapeutic significance of distal airway inflammation in asthma. J Allergy Clin Immunol 2002;109:S447-S460.
12. Shaw RJ, Djukanovic R, Tashkin DP, Millar AB, du Bois RM, Orr PA. The role of small airways in lung disease. Respir Med 2002;96:67-80.
13. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. Eur Respir J 1997;10:292-300.
14. Carroll N, Carello S, Cooke C, James A. Airway structure and inflammatory cells in fatal attacks of asthma. Eur Respir J 1996;9:709-715.
15. Hamid QA. Peripheral inflammation is more important than central inflammation. Respir Med 1997;91(Suppl A):11-12.
16. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004; 350:2645–2653.
17. Macklem PT, Mead J. Resistance of central and peripheral airways measured by a retrograde catheter. J Appl Physiol 1967;22:395-401.
18. Brown R, Woolcock AJ, Vincent NJ, Macklem PT. Physiological effects of experimental airway obstruction with beads. J Appl Physiol 1969;27:328-335.
19. Acerbi D, Brambilla G, Kottakis I. Advances in asthma and COPD management: delivering CFC-free inhaled therapy using Modulite technology. Pulm Pharmacol Ther 2007; 20:290-303.
20. Leach CL, Davidson PJ, Hasselquist BE, et al. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers. Chest 2002; 122:510-516.
21. Thongngarm T, Silkoff PE, Kossack WS, Nelson HS. Hydrofluoroalkane-134A beclomethasone or chlorofluorocarbon fluticasone: effect on small airways in poorly controlled asthma. J Asthma 2005;42:257-263.
22. Goldin JG, Tashkin DP, Kleerup EC, et al. Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: assessment with functional helical thin-section computed tomography. J Allergy Clin Immunol 1999; 104:S258-67.
23. Rigamonti E, Kottakis I, Pelc M, Grzelewska-Rzymowska I, Feschencko Y. Comparison of a new extra-fine beclomethasone dipropionate HFA134a-formulated pMDI with a standard BDP CFC pMDI in adults with moderate persistent asthma. Eur Respir J 2006; 28(Suppl. 50):206s.
24. Busse WW, Brazinsky S, Jacobson K, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol 1999; 104:1215-22.
25. Barnes N, Price D, Colice G, et al. Asthma control with extrafine-particle hydrofluoroalkane-beclometasone vs. large-particle chlorofluorocarbon-beclometasone: a real-world observational study. Clin Exp Allergy 2011.
26. Juniper E, Price DB, Stampone PA, Creemers JPHM, Mol SJM, Fireman P. Clinically important improvements in asthma-specific Quality of Life, but no difference in conventional clinical indexes in patients changed from conventional beclomethasone dipropionate approximately half the dose of extrafine beclomethasone dipropionate. Chest 2002; 121:1824-32.
27. Bousquet J, Poli G, Acerbi D, Monno R, Ramael S, Nollevaux F. Systemic exposure and implications for lung deposition with an extra-fineHFA beclometasone dipropionate-formoterol fixed combination. Clinical Pharmacokinet. 2009; 48:347–358.
28. De Backer W, Devolder A, Poli G, et al. Lung Deposition of BDP=Formoterol HFA pMDI in Healthy Volunteers, Asthmatic, and COPD Patients. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2010; 23:1-12.
29. Scichilone N, Battaglia S, Sorino C, et al. Effects of extra-fine inhaled beclomethasone/formoterol on both large and small airways in asthma. Allergy 2010;65:897-902.
30. Huchon G, Magnussen H, Chuchalin A, Dymek L, Gonod FB, Bousquet J. Lung function and asthma control with beclomethasone and formoterol in a single inhaler. Respir Med 2009; 103:41-49.
31. Haughney J, Price D, Kaplan A, et al. Achieving asthma control in practice: understanding the reasons for poor control. Respir Med 2008; 102:1681-1693.
32. Thomson NC, Chaudhuri R. Asthma in smokers: challenges and opportunities. Curr Opin Pulm Med Jan 2009; 15:39-45.
33. Invernizzi G, Ruprecht A, De Marco C, Mazza R, Nicolini G, Boffi R. Inhaled steroid/tobacco smoke particle interactions: a new light on steroid resistance. Respir Res Jun 11 2009; 10:48.
34. Allegra L, Cremonesi G, Girbino G, et al. Real-life prospective study on asthma control in Italy: Cross-sectional phase results. Respir Med 2012; 106:205-214.
35. Brusselle G, Peche R, Van de Brande P, Verhulst A, Hollanders W, Bruhwyler J. Real-life effectiveness of extrafine beclomethasone diporpionate/formoterol in adults with persistent asthma according to smoking status. Respir Med 2012.
36. Chawes BLK, Piccinno A, Kreiner-Møller E, et al. Pharmacoki-

netic comparison of inhaled fixed combination *vs*. the free combination of beclomethasone and formoterol pMDIs in asthmatic children. Br J Clin Pharmacol 2012; 75:1081-1088.
37. Calverley PMA, Kuna P, Monso E, et al. Beclomethasone/formoterol in the management of COPD: A randomised controlled trial. Respir Med 2010; 104:1858-1868.
38. Vos W, De Backer J, Poli G, et al. Novel Functional Imaging of Changes in Small Airways of Patients Treated with Extrafine Beclomethasone/Formoterol. Respiration 2013;
39. Singh D, Corradi M, Bindi E, Baronio R, Petruzzelli S, Paggiaro P. Relief of methacholine-induced bronchospasm with extrafine beclomethasone dipropionate/formoterol in comparison with salbutamol in asthma. Pulm Pharmacology and Therapeutics 2012; 25:392-398.
40. Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med 2013; 1:23-31.
41. Contoli M, Bousquet J, Fabbri LM, et al. The small airways and distal lung compartment in asthma and COPD: a time for reappraisal. Allergy 2010; 65:141-151.
42. Scichilone N, Battaglia S, Olivieri D, Bellia V. The role of small airways in monitoring the response to asthma treatment: what is beyond FEV1? Allergy 2009; 64:1563-1569.
43. Popov TA, Petrova D, Kralimarkova TZ, et al. Real life clinical study design supporting the effectiveness of extra-fine inhaled beclomethasone/formoterol at the level of small airways of asthmatics. Pulmonary Pharmacology & Therapeutics 2013;
44. Dempsey OJ, Wilson AM, Coutie WJR, Lipworth BJ. Evaluation of the effect of a large volume spacer on the systemic bioactivity of fluticasone propionate metered-dose inhaler. Chest 1999; 116:935–940.
45. Singh D, Collarini S, Poli G, Acerbi D, Amadasi A, Rusca A. Effect of AeroChamber Plus™ on the lung and systemic bioavailability of beclometasone dipropionate/formoterol pMDI. Br J Clin Pharmacol 2011; 72:932-939.
46. Corradi M, Chrystyn H, Cosio BG, et al. NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclometasone and formoterol to treat large and small airways in asthma. Expert Opin Drug Deliv 2014; 12:1-10. [Epub ahead of print]