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Improved control of asthma symptoms with a reduced dose of HFA-BDP extrafine aerosol: an open-label, randomised study

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Abstract. – ***Background:*** **Extrafine aerosols may improve asthma symptom control through increased lung deposition of medication to inflamed peripheral airways.**

Methods: **The effect of switching patients with asthma maintained on up to 2000 µg/day chlorofluorocarbon-beclomethasone dipropionate (CFC-BDP), 1600 µg/day budesonide, 1000 µg/day fluticasone, or 2000 µg/day flunisolide, to a reduced dose of hydrofluoroalkane-134a BDP (HFA-BDP) extrafine aerosol (maximum 800 µg/day) was investigated during an open-label multicentre study. Following a 7–14-day run-in on previous medication, 716 patients were randomised to 24 weeks' treatment with an appropriate reduced dose of HFA-BDP.**

Results: **Morning peak expiratory flow (AM PEF) measurements showed that, after 24 weeks, the reduced dose of HFA-BDP maintained equivalent lung function compared with all previous medications. Furthermore, asthma symptom scores revealed improvements across all groups and the proportion of symptom free days and nights and beta-agonist free days increased significantly ($p < 0.05$) in all but one group. Quality of life improved with 80% of patients reporting goo/very good overall asthma control compared with 70% previously. Treatment-associated adverse events were generally infrequent, mild and transient.**

Conclusions: **Patients on conventional inhaled corticosteroids may reduce their daily steroid dose to 800 µg or less whilst maintaining lung function and improving asthma symptom control by using the extrafine aerosol of HFA-BDP.**

Key Words:

Asthma, HFA-BDP, Autohaler™, Corticosteroid, QVAR™, Ventolair™.

Introduction

The particle size of inhaled corticosteroids (ICS) is an important determinant for delivery of asthma medication to the lung. On inhalation, larger particles are more likely to impact in the oropharynx, while particles of narrower diameter have a greater chance of reaching the major sites of inflammation in the smaller bronchial airways[1]. HFA-BDP (Qvar™/ Ventolair™; 3M Medica) contains a well-known pharmaceutical compound, beclomethasone dipropionate (BDP), the administration of which has been optimised through the use of a new chlorofluorocarbon (CFC)-free propellant, hydrofluoroalkane-134a (HFA). In the new inhaler, the BDP is present in a solution, rather than a suspension of propellant. As a result of this reformulation and other technical improvements, particles of HFA-BDP, delivered from either a metered-dose inhaler (MDI) or a breath-actuated Autohaler™ inhalation device, have a mean mass aerodynamic diameter (MMAD) of approximately 1 µm[2,3]. This compares favourably with particles delivered from conventional BDP, budesonide, fluticasone, and flunisolide CFC-based MDIs and dry powder inhalers (DPIs), for which the MMAD has been shown to range from 2–5 µm[4-8]. As a consequence, the fine particle fraction (i.e. the proportion of nominal dose capable of penetrating the lung airways) is greater for HFA-BDP compared with traditional ICS[6]. Radiolabelled lung deposition studies with HFA-BDP and

CFC-BDP, in both healthy volunteers and patients with asthma, have confirmed that this greater fine particle fraction translates into more efficient delivery to the lung airways; approximately 60% of an ex-actuator HFA-BDP dose reaches the lungs compared with less than 10% from a CFC-BDP inhaler[3,5,9]. Furthermore, HFA-BDP particles are distributed throughout the large, intermediate and small lung airways, differing from the lung deposition of the larger particles of CFC-BDP, which are predominantly distributed in the central region[10].

Successful clinical management of asthma requires adequate delivery of the inhaled drug to the active disease sites in the lung[11,12]. Given that anti-inflammatory medications are thought to be most effective when deposited in the smaller airways[13], the improved delivery characteristics of extrafine aerosols like HFA-BDP may offer clinical benefits, such as improved symptom control at lower daily steroid loads. Indeed, several randomised controlled studies have shown that equivalent asthma control can be achieved if the BDP dose necessary in CFC MDI systems is reduced by a factor of 2.5 when using HFA-BDP[14-16]. It is logical, therefore, that the smaller particle size of HFA-BDP should also permit enhanced lung deposition compared with other conventional ICS of larger particle size. As such, a similar pattern of equivalent asthma control should emerge with lower doses of HFA-BDP. This study was undertaken to test this hypothesis.

The primary objective was to determine whether patients with asthma symptoms maintained on CFC-BDP, budesonide (delivered via a CFC-based MDI or DPI), fluticasone (from a CFC or HFA-based MDI), or flunisolide, could reduce their daily ICS dose during a switch to HFA-BDP and maintain asthma control. Dosing ratios for each ICS were deduced from the established relative potencies for each drug[17,18] and previous comparative studies between inhalers[14,19-22]. To facilitate medication delivery, the Autohaler™, which minimises patient handling difficulties such as poor actuation/inhalation coordination[23], was chosen as the delivery device for HFA-BDP.

Methods

This was a 24-week, open-label comparative study conducted at 108 centres in Germany. The study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki (amended South Africa, 1996) and was approved by local ethics review committees at each study site. All patients provided informed written consent.

Patients

The study population included adults, aged 18 to 75 years, with a clinical diagnosis of asthma and a peak expiratory flow (PEF) of ≥ 50% of the predicted normal, according to Nunn and Gregg[24]. To be eligible for inclusion, study participants must have been maintained on one of the ICS listed in Table I for at least 4 weeks prior to enrolment, whilst using a short-acting beta-agonist as rescue medication on an as-needed basis. Subjects had to have demonstrated asthma reversibility within the past 24 months, through either an improvement of PEF ≥ 15% or forced expiratory volume in one second (FEV_1) ≥ 12% 10 minutes after administration of 200 µg salbutamol, or equivalent. Individuals not meeting these criteria, and those with any clinically significant abnormality or disease, particularly respiratory disorders other than asthma, acute respiratory tract infections within the past 2 weeks or during the run-in period, cardiac arrhythmia or disease, or clinically visible oral candidiasis, were not included in the study. Subjects were also excluded if they

Table I. Equivalent doses (µg/puff) of HFA-BDP and conventional inhaled corticosteroids.

Previous treatment	Previous dosage (µg/puff)	Corresponding HFA-BDP dosage (µg/puff)
CFC-BDP	100	50
CFC-BDP	250	100
CFC-budesonide	200	100
Budesonide Turbuhaler®	200	100
Fluticasone MDI*	125	100
CFC-flunisolide	250	100

* CFC or HFA propellant.

were pregnant or breast-feeding, if they had recently used steroid-based products, if they had received long-term antibiotics, monoamine oxidase inhibitors, tricyclic antidepressants, or another investigational study drug within the past 4 weeks, of if they had a known hypersensitivity or idiosyncratic reaction to sympathomimetic drugs or ICSs. Use of short-acting beta-agonists on an as-needed basis, and constant (not varying) doses of inhaled combination products without steroids, long-acting beta-agonists, anti-cholinergic agents, theophylline and immunotherapy, were permitted throughout the study.

Study Design

After an initial screening visit that included a physical examination and a relevant medical history, eligible patients underwent a 7–14-day run-in period during which time they continued to take their previous asthma medication. Asthma symptom control was assessed throughout this period by daily patient diary recordings of PEF on awakening (AM PEF) and before retiring (PM PEF), asthma symptom and sleep disturbance scores, and beta-agonist use. Patients demonstrating adequate diary compliance and correct use of a peak flow meter were entered into a 24-week treatment phase receiving HFA-BDP, via the Autohaler™ inhalation device, at an appropriate lower dose corresponding to their previous ICS treatment (Table I); the maximum daily dosage of HFA-BDP was 800 µg. In total, patients made six clinic visits – screening at week –1, allocation to study treatment at week 0 (baseline), and at weeks 6, 12, 18 and 24 during the treatment phase. Correct use of the HFA-BDP Autohaler™ was demonstrated at baseline using a placebo device and was reviewed at subsequent clinic visits.

Assessments

Throughout the study, the following parameters were recorded daily in patients' diaries: AM PEF, PM PEF, use of short-acting beta-agonist, and asthma symptoms and sleep disturbance. PEF measurements were made using a mini-Wright peak flow meter at the same time each day, before medication administration. Patients were instructed to make three measurements at each time point and record the maximum value in their diary. Daytime symptoms of wheezing, shortness of breath, chest tightness and cough were rated on a scale of 0 to 5 (0 = not present, 5 = so severe that the patient could not attend work or carry out normal daily activities) and symptoms during the night were assessed on a scale of 0 to 4 (0 = no symptoms during the night, 4 = asthma symptoms so severe that the patient did not fall asleep at all). In addition, patients completed a quality of life questionnaire at the baseline clinic visit in order to describe the frequency and severity of their asthma symptoms and the quality of asthma control achieved with their previous inhaler. The questionnaire included three domains: (1) "disturbance at night caused by asthma", rated on a scale of 0 to 4 (0 = no asthma symptoms during most of the nights, 4 = sleepless due to asthma during the whole of the night); (2) "asthma symptoms in the morning", assessed on a scale of 0 to 5 (0 = symptom-free most mornings, 5 = symptoms so severe that no normal daily activity possible); (3) "asthma control", ascertained on a 5-point scale ranging from "very good" to "insufficient". At subsequent clinic visits, asthma control on HFA-BDP was evaluated using the same 5-point scale. The frequency of asthma symptoms in the morning and disturbances at night were compared between the two inhalers using a 5-point scale, ranging from "strongly reduced" to "strongly increased". Regarding safety, adverse events were reviewed and assessed by the investigator at each clinic visit. Specific questions were asked about the incidence of oropharyngeal candidiasis, dysphonia, urgent medical care for asthma symptoms and hospitalisations.

Patient compliance with their study medication regimen was assessed by weighing the inhaler canisters before and after use, and calculating the respective number of dispensed doses. A patient was considered to have been compliant if the total number of actuations was ± 40% of planned.

Statistical Analysis

All analyses were performed on the intent-to-treat (ITT) population (i.e. all individuals who received at least one dose of HFA-BDP and had at least one diary record of PEF). The primary efficacy variable – the

mean change from baseline in AM PEF after 12 weeks' treatment with HFA-BDP – was analysed for each of the four pre-treatment groups. The Westlake method was used to demonstrate the equivalence of the pre- and study treatment; confidence intervals (CIs) were calculated for the mean change from baseline in AM PEF for each group. Based on the results of a previous study[16] the standard deviation (SD) of the change in AM PEF from baseline to 12 weeks was assumed to be approximately 51 L/min. Treatments were considered to be equivalent, therefore, if the 95% CI for the mean difference between AM PEF at baseline (i.e., on pre-treatment) and AM PEF after 12 weeks' treatment with HFA-BDP was within ± 25 L/min. Bonferroni-Holm adjustments were made to account for multiple comparisons. A sample size of approximately 750 patients was deemed necessary to test the study hypothesis, assuming a standard deviation of 51 L/min, a power of 90% and $\alpha = 0.0125$. An analysis of covariance (ANCOVA) model was used to test differences between the pre-treatment groups for secondary efficacy parameters and Student's t-tests were performed to evaluate changes from baseline (alpha = 0.05, two-sided).

Results

Patients

In total, 726 eligible patients entered the treatment period. Of these, 716 individuals received at least one dose of study medication and recorded at least one AM PEF value during treatment and, as such, were included in the ITT study population.

Subjects were allocated into groups according to their previous asthma medication: CFC-BDP, budesonide, fluticasone, and flunisolide. Baseline asthma symptoms were low, although large SD values indicated a wide range of symptom severity in all pre-treatment groups. Patient characteristics were similar with no significant differences between the groups regarding age, sex, lung function, reversibility or airflow limitation, percentage of days and nights free from asthma symptoms, or short-acting beta-agonist use (Table II).

In total, 63.4% of patients had taken their previous ICS using an MDI or Autohaler™, while 36.2% had used a dry powder inhaler (DPI) to administer medication. Of those patients using an MDI, 47.8% also used a spacer device. Most patients (87.3%) had been reliant on beta-agonists for rescue medication. The previous mean (SD) ICS daily doses were CFC-BDP 881.6 µg (292.9 µg), budesonide

Table II. Baseline demographics (ITT population, n = 716).

	SUBGROUPS BASED ON PREVIOUS STEROID USE			
	CFC-BDP (n = 178)	Budesonide (n = 317)	Fluticasone (n = 145)	Flunisolide (n = 76)
Male/female ratio (%)	43/57	40/60	50/50	38/62
Age (years)	46.9 (14.8)	47.5 (14.9)	47.6 (14.5)	48.7 (13.7)
Asthma reversibility (% patients)				
PEF ≥ 15%	23.0	38.5	35.9	23.7
FEV_1 ≥ 12%	32.6	23.0	20.7	31.6
Asthma history (years)	9.7 (10.2)	10.8 (12.0)	10.6 (11.8)	11.1 (13.4)
Smokers (% patients)	13.5	17.4	9.0	10.5
Beta-agonist use (n/day)	1.4 (1.5)	1.7 (2.0)	1.5 (2.0)	1.7 (2.4)
Beta-agonist free days (% days)	49.8	45.4	51.3	50.7
AM PEF (L/min)	364.0 (108.1)	354.3 (104.5)	360.2 (112.3)	347.7 (117.5)
PM PEF (L/min)	377.7 (108.8)	368.5 (108.6)	374.9 (118.5)	363.3 (119.0)
AM PEF (% predicted normal)	69.0 (16.2)	67.9 (15.9)	67.3 (17.6)	66.8 (19.2)
Asthma symptom scores				
Wheezing	0.5 (0.7)	0.7 (0.9)	0.6 (0.9)	0.6 (1.0)
Shortness of breath	0.8 (0.9)	1.0 (1.1)	1.0 (1.1)	1.1 (1.2)
Chest tightness	0.4 (0.7)	0.6 (0.8)	0.6 (1.0)	0.7 (1.0)
Cough	0.6 (0.9)	0.9 (1.0)	0.9 (1.0)	0.9 (1.1)

Values are given as mean (SD), unless otherwise stated.

678.9 µg (223.2 µg), fluticasone 322.4 µg (122.1 µg), and flunisolide 859.9 µg (282.4 µg). In total, 51.8% of patients were deemed to have been compliant with the prescribed HFA-BDP dosing regimen. In these patients, the actual mean (SD) dosing ratios were in close agreement with those recommended in Table I: CFC-BDP 2.8 (0.6), budesonide 2.3 (0.5), fluticasone 1.3 (0.3), and flunisolide 2.5 (0.6).

Seventy patients withdrew from the study prematurely. The main reasons for discontinuation were adverse, events, loss to follow-up and violation of study entry criteria.

Asthma Control

The mean changes in AM PEF and PM PEF after switching to a lower dose of HFA-BDP are summarised in Table III. Equivalent efficacy was demonstrated between HFA-BDP and pre-treatment with CFC-BDP, budesonide, fluticasone or flunisolide at weeks 12 and 24, indicated by the confinement of the CI of the mean change from baseline in AM PEF within the pre-defined equivalence range (± 25 L/min). Similar results were observed for PM PEF.

The proportion of symptom free days and nights increased throughout the study in all treatment groups after switching to a reduced dose of HFA-BDP. The differences were statistically significant at week 24 compared with previous treatment for all groups, with the exception of symptom free nights in the flunisolide group (Figure 1). All groups showed an increase to more than 50% in symptom free days on the new treatment. Furthermore, after 24 weeks' treatment with HFA-BDP, more than 79% of nights were reported to be free of sleep disturbance due to asthma symptoms in all treated groups. Examination of asthma symptom scores revealed minor improvements for each treatment group on all symptoms after 24 weeks' HFA-BDP administration. Improvements were statistically significant for the majority of parameters in the groups previously treated with CFC-BDP and budesonide (Figure 2). Sleep disturbance scores decreased slightly in all groups by 0.1 at week 24; these reductions were significant in the CFC-BDP and budesonide pre-treatment groups ($p < 0.05$).

Patients used short-acting beta-agonist rescue medication, on average, 0.9 to 1.7-times during each 24-hour day of the study. A moderate reduction was noted in use after 24 weeks' treatment with HFA-BDP compared with use on previous medication; the mean change from baseline was significant for the CFC-BDP (–0.3), budesonide (–0.3) and flunisolide (–0.6) groups ($p < 0.05$), but not in the fluticasone group (–0.2). There was also a significantly greater percentage of beta-agonist free days at week 24 compared with baseline in all pre-treatment groups ($p < 0.05$; Table III); an overall increase of greater than 10%, from 48.3% to 58.6% beta-agonist free days.

Table III. Mean change from previous treatment in AM and PM PEF and percentage of beta-agonist free days following switch to HFA-BDP; subgroups based on previous steroid use (ITT population, n = 716).

	SUBGROUPS BASED ON PREVIOUS STEROID USE BEFORE SWITCH TO HFA-BDP			
	CFC-BDP (n = 178)	Budesonide (n = 317)	Fluticasone (n = 145)	Flunisolide (n = 76)
Δ AM PEF (L/min)†				
Week 12	3.9 (–5.2, 13.0)	6.4 (–1.7, 14.5)	2.0 (–9.7, 13.6)	4.2 (–9.3, 17.6)
Week 24	9.8 (–1.5, 21.2)	6.5 (–0.9, 13.9)	4.8 (–8.7, 18.3)	–4.9 (–20.3, 10.6)
Δ PM PEF (L/min)†				
Week 12	1.4 (–6.3, 9.1)	7.8 (1.5, 14.0)	0.9 (–8.9, 10.6)	–1.1 (–12.6, 10.4)
Week 24	9.3 (–2.0, 20.6)	5.8 (–1.7, 13.2)	–1.3 (–15.6, 13.1)	–7.6 (–21.0, 5.8)
Δ beta-agonist free days (%)‡				
Week 12	5.5 (39.7)	2.7 (35.1)	7.9 (31.9)*	15.1 (40.0)*
Week 24	12.1 (40.8)*	7.6 (38.6)*	7.7 (39.6)*	11.9 (36.1)*

† Values are mean (CI); ‡ values are mean (SD); * $p < 0.05$ on HFA-BDP vs. previous ICS.

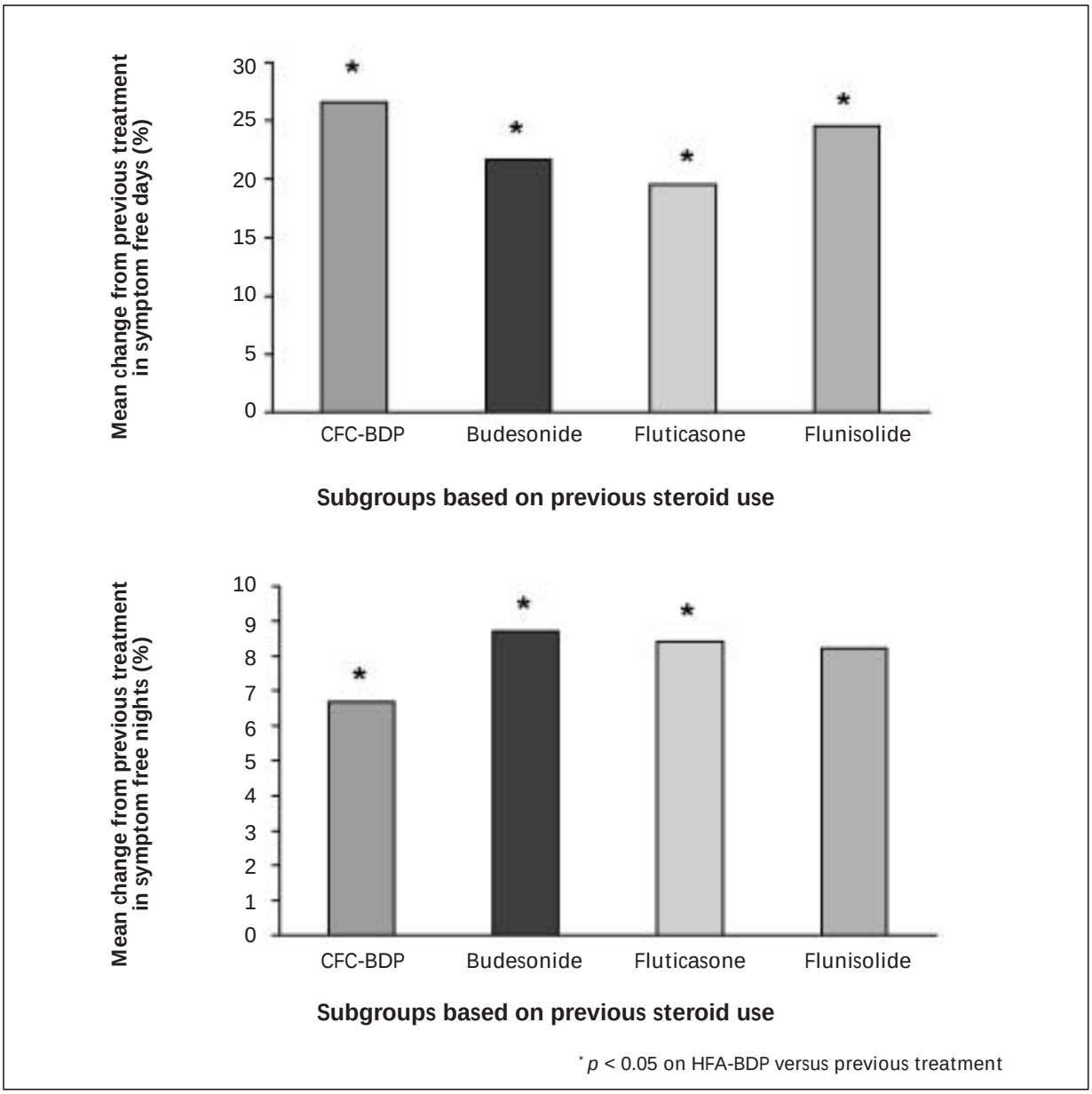

Figure 1. Mean change from previous treatment in % symptom free days and nights after 24 weeks' HFA-BDP treatment; subgroups based on previous steroid use (ITT population, n = 716).

Quality of Life

In general, quality of life improved in patients when they were switched to a lower dose of HFA-BDP. At baseline, 68.5% of patients reported very good / good asthma control with their former inhaler. However, 34.5% of the study population reported asthma symptoms of varying severity in the morning. In addition, 66.9% of patients reported that their asthma symptoms caused sleep disturbance, ranging in severity from a single awakening during the night, to sleeplessness. After 24 weeks' treatment with HFA-BDP, nearly half of the study participants reported a reduction of symptoms, both in the morning (48.3% patients) and during the night (46.5% patients); the proportion of subjects was similar for each pre-treatment group. When asked to compare asthma control on their previous medication with that experienced on HFA-BDP, the percentage of patients reporting good or very good control

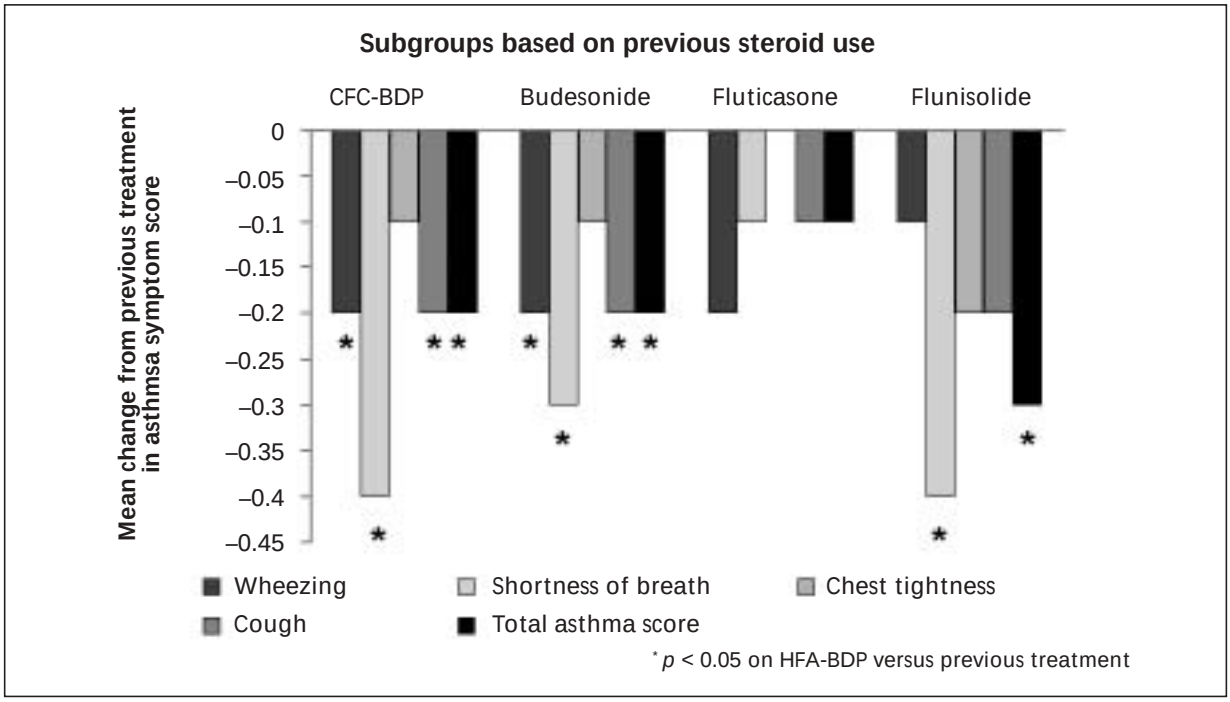

Figure 2. Mean change from previous treatment in asthma symptom scores after 24 weeks' HFA-BDP treatment; subgroups based on previous steroid use (ITT population, n = 716).

had increased to 81.3%. The beneficial effect was most pronounced in the budesonide (79.8% versus 63.7% at baseline) and fluticasone (75.9% versus 69.7% at baseline) pre-treatment groups.

Safety Evaluations

Adverse events considered to be associated with HFA-BDP occurred in 107 (14.7%) patients. The most common were comments associated with inhaling the spray and respiratory system disorders, occurring in 89 (12.3%) and 17 (2.3%) patients, respectively. Dysphonia occurred in 52 (7.2%) patients and oropharyngeal candidiasis in 39 (5.4%) patients. These events were solicited during patient interviews. All adverse events were generally low to moderate in intensity. Serious adverse events were rare, occurring in only 19 (2.6%) patients; none was related to study medication. In total, 31 (4.3%) patients withdrew from the study because of adverse events, most commonly because of increased asthma symptoms (11 patients; 1.5%), dyspnoea (7 patients; 1.0%), and bronchitis (5 patients; 0.7%). Results were similar across all pre-treatment groups.

Discussion

Clinical studies remain the "gold standard" for the demonstration of therapeutic equivalence of inhaled products for the treatment of asthma[25]. The present study was designed to evaluate if a reduction in daily steroid load could be achieved in patients changing from conventional ICS, including CFC-BDP, budesonide, fluticasone and flunisolide to HFA-BDP, whilst maintaining control of asthma symptoms. A reduced dose of HFA-BDP was proposed for each pre-treatment group, based on the assumption that HFA-BDP would provide equivalent asthma control at a significantly lower dose owing to improved delivery of the drug to inflamed areas of the lungs, particularly the peripheral airways – a result of its smaller particle size (approximately 1 µm versus 2–5 µm)[6]. Previous randomised controlled clinical studies have already demonstrated that, in comparison with conventional CFC-BDP formulations, it is possible to achieve a dose reduction of approximately 2.5-fold with HFA-BDP, while maintaining the same level of asthma control[14,15]. Whether this can be attributed to im-

proved central airway deposition with HFA-BDP has yet to be definitively proven, however, direct radiolabelled deposition studies in both healthy volunteers and patients with asthma revealed ex-actuator lung deposition to be approximately 60% with HFA-BDP compared with less than 10% with CFC-BDP[3,5]. Furthermore, Goldin and colleagues used functional high-resolution computed tomography to assess the relative efficacy of HFA-BDP and CFC-BDP on regional air trapping – an indirect measure of small airways function and regional hyperreactivity[26]. Air trapping was statistically significantly reduced following methacholine challenge in patients receiving HFA-BDP compared with those taking CFC-BDP. These results would appear to suggest that HFA-BDP has greater efficacy than CFC-BDP in the small peripheral airways.

While limited in its open-label nature and lack of placebo group, the design of this study and the broad range of asthma severity, reflected by the initial ICS doses on which patients were previously maintained, is representative of treatment practices in a normal clinical setting in which patients might be switched from conventional ICS therapy to HFA-BDP. However, the open design may also have introduced the potential for bias against previous treatments and against the new inhaler depending on individual patients' perceptions towards a treatment change. Furthermore the run-in period, during which time patients were assessed on their previous medication, was relatively short and may not have provided an accurate representation of patient compliance on previous medication.

The doses recommended for the switch to HFA-BDP in this study were based on the published literature. In choosing the exact dosing ratio for each previous ICS, factors taken into consideration included the known relative potencies of BDP, budesonide, fluticasone, and flunisolide[17,18], the established 2.5-fold dosage reduction recommended when switching from CFC-BDP to HFA-BDP[14-16], the results of two randomised clinical studies, which demonstrated the therapeutic equivalence of HFA-BDP 800 µg/day with budesonide Turbuhaler® 1600 µg/day and HFA-fluticasone 1000 µg/day[19,22], and the results of two randomised clinical studies, which demonstrated the therapeutic equivalence of HFA-BDP 400 µg/day with budesonide Turbuhaler® 800 µg/day and fluticasone 400 µg/day, respectively[20,21].

The breath-actuated Autohaler™ inhalation device was chosen to administer HFA-BDP in this investigation. This device incorporates a mechanism activated automatically during inspiration that triggers the release of a metered dose, enabling reproducible and consistent delivery of asthma medication early during an inhalation across a wide range of inspiratory flows[23,27]. It is well known that a large proportion (up to 50%) of patients experience difficulties in coordination of inspiration and actuation when using MDIs[28]. This can lead to poor drug delivery, decreased disease control, and increased inhaler use. The Autohaler™ was chosen, rather than the MDI, in an attempt to facilitate medication delivery and reduce interpatient variability in dosage administration. This choice was particularly relevant considering that nearly 50% of patients in this study who had previously been using an MDI were also reliant on the use of a spacer, potentially indicating problems with inhaler handling. The study protocol also ensured that correct use of the new HFA-BDP inhaler was demonstrated at baseline and reviewed at subsequent clinic visits.

The results of this study confirm the findings from previous clinical trials that maintenance of asthma control is possible with HFA-BDP despite a 2.5-fold reduction in steroid load compared with CFC-BDP[14-16]. Following administration of a reduced dose of HFA-BDP, pulmonary function, as assessed by AM PEF, was found to be equivalent to that recorded on up to 2000 µg/day CFC-BDP. Similarities in study design allow meaningful comparisons with the results of an 8-week open-label study in which patients with stable asthma were successfully switched from existing treatment on CFC-BDP 400–1600 µg/day to approximately half the daily dose of HFA-BDP[28]. This investigation is novel, however, in that it also clearly demonstrates that a reduced dose of HFA-BDP (up to a maximum of 800 µg/day) maintained equivalent control of pulmonary function when compared with previous treatment with up to 1600 µg/day

budesonide, 1000 µg/day fluticasone or 2000 µg/day flunisolide throughout the 24-week treatment period. Notably, with the exception of the flunisolide group at week 24, mean AM PEF values increased slightly over the time course of the study in all groups, which may indicate a trend towards improved asthma control on HFA-BDP despite reduced steroid load. Furthermore, some of the secondary efficacy parameters also improved on switching to HFA-BDP. In particular, there were statistically significant increases in the number of days and nights free from asthma symptoms and a statistically significant decrease in the use of short-acting beta-agonist medication compared with baseline. A further improvement in control of asthma symptoms on switching from conventional ICS to a reduced dose of HFA-BDP is an exciting finding that has also been reported in two other studies with HFA-BDP and CFC-BDP. During a 6-month double-blind investigation, patients with well-controlled asthma on CFC-BDP 1500 µg/day or equivalent were randomised to receive treatment with HFA-BDP 800 µg/day or to continue on CFC-BDP 1500 µg/day[29]. Changes from baseline in the percentage of days without wheeze, cough, shortness of breath and chest tightness were statistically significantly greater at all time-points for patients on HFA-BDP compared with CFC-BDP. In a second study – a 12-month open-label, parallel-group investigation – patients were randomised to receive CFC-BDP (400–1600 µg/day) or HFA-BDP at approximately half the daily dose in a 1:3 ratio[30]. The proportion of patients with increased asthma symptoms was slightly higher for patients receiving CFC-BDP than HFA-BDP during each 2-month interval throughout the study. The additional symptom control observed during these studies may reflect the improved lung delivery characteristics of HFA-BDP, in particular the increased delivery of BDP to the peripheral airways.

In agreement with the results from conventional indices of pulmonary function and asthma symptom control in this study, improved quality of life scores were also observed following the switch to a reduced dose of HFA-BDP. Nearly half of all patients reported a reduction in asthma symptoms in the morning and at night, and there was an increase of more than 10% in the number of patients rating asthma control as "good" or "very good" compared with their previous inhaler. These results are paramount given that one of the major goals in the treatment of asthma is to improve the functioning and well-being of the patient. Determination of quality of life ensures that the patient's perceptions of effectiveness are considered in addition to clinical benefit. Two previous clinical studies have assessed changes in quality of life when switching from CFC-BDP to a reduced dose of HFA-BDP[31,32]. The results from both investigations are consistent with this study. In a 12-week, parallel-group, multicentre trial, HFA-BDP 400 µg/day was as effective as CFC-BDP 800 µg/day in sustaining improvements in quality of life on the Asthma Quality of Life Questionnaire (AQLQ) following withdrawal of 7–12 days of prednisolone treatment in patients with moderate asthma[31]. In a more recent open-label, parallel-group investigation, clinically important improvements in AQLQ score were observed for HFA-BDP versus CFC-BDP after 12 months, despite approximately half the daily steroid dose[32]. Pulmonary function and asthma control were similar for both groups. These results are particularly interesting as quality of life is also becoming accepted as an important evaluation in the cost-effectiveness of therapy[33].

HFA-BDP treatment was well tolerated in this study. The maximum intensity of dysphonia and oropharyngeal candidiasis was generally low to moderate and the frequency of these events was as expected with conventional ICS, despite the fact that the incidence of events were solicited by investigators during clinic visits, thus increasing their chance of being reported. It has been suggested that increased lung deposition with extrafine aerosols might be associated with a higher incidence of systemic adverse events; however, a similar safety profile has previously been reported for HFA-BDP and CFC-BDP, notably with no differences in systemic effects[29,30] or respiratory events leading to hospital admissions[34].

In summary, asthma control in patients receiving a reduced dosage of HFA-BDP according to the switching recommendations outlined in this study was equivalent

to asthma control achieved by conventional treatment with CFC-BDP, budesonide, fluticasone, and flunisolide. Patients needing up to 2000 µg CFC-BDP, 1600 µg budesonide, 1000 µg fluticasone or 2000 µg flunisolide per day were able to reduce their daily ICS dose to HFA-BDP 800 µg or less, whilst maintaining improvements in pulmonary function and experiencing an increase in their symptom control. These findings support the hypothesis that reformulation of BDP in HFA propellant achieves at least equivalent efficacy at lower total daily steroid load while providing improved therapeutic outcomes over traditional ICS formulations, as demonstrated by improved symptom control for individual patients.

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