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Asthma Control with Inhaled Corticosteroids in the Typical Clinical Setting

Denver - Prospective, carefully controlled randomized clinical trials often exclude the very patients that are seen by most general practitioners. Retrospective rigorously conducted observational studies look closely at patients who have been treated in more typical clinical settings. As presented here at the ATS, studies from the UK and US used large patient record databases to evaluate dosages and outcomes of treatments with 2 inhaled corticosteroids. Investigators also determined whether physicians are following recommended asthma treatment guidelines. Other researchers considered whether adding a small particle inhaled corticosteroid would benefit patients whose asthma was not being adequately controlled on a combination medication and looked more closely at the impact of inhaled corticosteroids on small airways function.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Québec

Of 2 commonly prescribed inhaled corticosteroid (ICS) therapies, fluticasone propionate (FP) and hydrofluoroalkane beclomethasone dipropionate (HFA-BDP), the former is more potent on a per μg basis while the latter provides a smaller particle size that leads to greater total and peripheral small airways deposition.

Delegates here at ATS learned of 3 recent retrospective studies from real world patient populations with asthma. Typical dosing and outcomes with these 2 agents were observed in settings that may be more reflective of everyday medical practice in the US and Canada than many controlled prospective trials.

Retrospective Analyses

A retrospective study of 1212 US patients ages 5 to 80 years who received step-up ICS therapy with HFA-BDP or FP drawn from the Ingenix Normative Healthcare Information Database assessed asthma control, exacerbation rate, respiratory-related hospitalizations and short-acting β_2-agonist (SABA) use over 1 year. Patients were matched by baseline demography and severity of disease and had comparable asthma control based on a baseline year of data prior to step-up.

Findings showed that physicians were not following US national (NHLBI) guidelines for asthma treatment, which advise a 1:1 dosing of HFA-BDP and FP. Patients received a lower daily dose of HFA-BDP than those on FP (median interquartile range [IQR]: 88 μg [44-153] and 145 μg [72-235] respectively; $P<0.001$). No differences were seen in primary outcomes of asthma control (OR 0.98; (95% CI, 0.75-1.27) and exacerbation (adjusted rate ratio 1.11; (95% CI, 0.91-1.45). Respiratory-related hospitalizations were comparable in the 2 groups, but SABA usage (>180 μg/day) was significantly lower among patients taking HFA-BDP than in those taking FP (20.5% vs. 28.1%, $P=0.003$).

Lead author Dr. Richard J. Martin, University of Colorado Health Sciences Center, Denver, stated, "Physicians in the US are increasing the dose of ICS when they should be adding long-acting β-agonist (LABA) treatment according to the national guidelines." He added that patients in the large database were matched by severity of disease and other variables and found that "Physicians prescribed FP at a significantly higher dose than HFA-BDP. [Yet] asthma control and other output variables were essentially the same or slightly better in the HFA-BDP group. So this particular study shows that physicians consider using HFA-BDP at a lower dose to achieve control."

Two larger, retrospective studies also assessed effectiveness of HFA-BDP and FP. Researchers evaluated asthma outcomes over 1 year in patients who initiated or increased ICS therapy with either agent. Confidence in real-life asthma ICS effectiveness studies will grow through validation of outcomes in different datasets. The UK study used data from the General Practice Research Database (n=2638), while the US data came from the Normative Healthcare Information Database (n=16,896). In each data set, patients were matched according to baseline demography and disease severity. Primary outcomes were asthma control and exacerbation rate ratio. Investigators also tracked total ICS daily dose and SABA use.

Baseline asthma control was the same between respective cohorts (i.e. those initiating ICS and those on step-up ICS). Across both studies, HFA-BDP was prescribed at lower doses than FP with comparable outcomes, including asthma control, exacerbation rate and SABA use.

As co-investigator, Dr. Martin commented, "The major take-home messages are twofold. First, in the real-world situation, physicians appear to prescribe inhaled FP at a much higher dose than HFA-BDP. We are not sure of the reasons for that. The second take-home message is very important: [patients] are using less inhaled steroid, [but] getting the same or better outcomes using HFA-BDP." Researchers also observed that notably higher SABA prescribing was recorded in the UK study, and found worse asthma control before ICS use was initiated in the US cohort.

Findings from a Canadian Private Practice Clinic

Dr. Warren Ramesh, Royal Alexandra Hospital, Edmonton, Alberta, led a study that reviewed patients from April 2002 through

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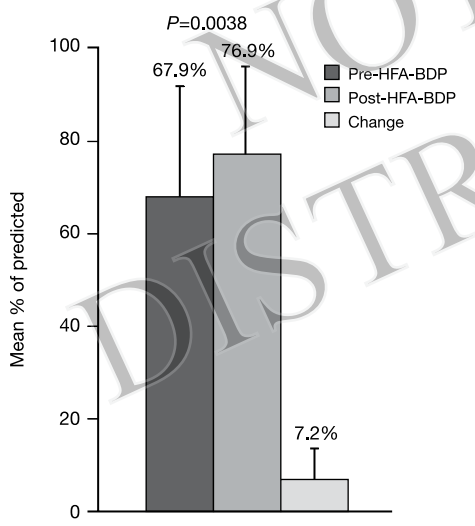
June 2010 from a private practice respiratory clinic in Canada. The researchers sought to determine whether patients who were inadequately controlled on an ICS/LABA combination treatment might benefit from the addition of HFA-BDP.

Eight patients with asthma met the inclusion criteria: age 18 to 90 years; prescribed ICS/LABA for at least 3 months prior to addition of HFA-BDP; prescribed HFA-BDP for at least 3 months in addition to ICS/LABA; and had spirometry results available ≥3 months prior to after addition of HFA-BDP. Mean prescribed dose of ICS was 971±71 µg and of LABA, 91±27 µg. Mean daily dose of add-on HFA-BDP was 338±92 µg.

There was a statistically significant increase in mean FEV_1 (% of predicted) after the addition of HFA-BDP (Figure 1). Five patients had ≥5% increase in FEV_1 (L) relative to pre-HFA-BDP, while 3 were unchanged. Six patients had ≥5% increase in FEF_{25-75} (L/sec), while 2 had ≥5% decrease, they both had ≥5% increase in FEV_1. All 8 patients reported improvement in ≥1 pulmonary symptoms (e.g. cough, shortness of breath, wheezing).

Figure 1. **Per Cent Increase of FEV_1**



Adapted from Ramesh et al. ATS 2011, abstract 20979.

Dr. Ramesh discussed the importance of these findings. "What we found from this small retrospective study is when patients are not controlled with maximum doses of ICS and LABA, adding a small-particle ICS may improve symptoms. Lung function seems to improve significantly as well." Investigators concluded that while the observations are limited by the retrospective nature of the study, lack of comparator population and a small number of patients, this novel combination approach might be useful in treating inadequately controlled asthma patients and should be evaluated in a prospective randomized study.

Small Airways Function

The small airways have been specifically implicated in the pathophysiology of asthma. Consequently, other investigators looked more closely at changes in small airways function in steroid-naive Japanese patients with mild-to-moderate asthma treated in a prospective randomized trial with either HFA-BDP or FP.

Consecutive steroid-naive patients with mild-to-moderate asthma were randomly assigned 200 µg b.i.d. open-label administration of HFA-BDP (n=31) or FP (n=29) for 12 weeks. Measurements included spirometry; impulse oscillometry (IOS); lung volumes; diffusion capacity; airway sensitivity and reactivity to methacholine; CT scanning with spirometric gating for central airway dimensions and small airway disease (air trapping); exhaled nitric oxide (eNO); induced sputum cells; and quality-of-life questionnaires.

Patients receiving HFA-BDP showed significantly greater improvement of airway sensitivity (P=0.008), diffusion capacity (DLCO; P=0.04), and a trend in alveolar fraction of eNO (P=0.056) compared with FP. FEV_1, sputum eosinophilia, bronchial fraction of eNO, luminal narrowing of central airways of CT, and almost all IOS and quality-of-life indices improved to a similar degree in both groups. CT scans revealed that wall thickness of large airways improved in the FP group, while small airway disease was unchanged in both groups.

Dr. Tomoshi Takeda, Department of Respiratory Medicine, Kyoto University Graduate School of Medicine, Japan, explained the results to ATS delegates, "Extra-fine ICS (HFA-BDP) has a more beneficial effect on the inflammation of small airways than the larger-particle ICS formulation, FP. We tried to check this by many methods—for example, [with] high-resolution CT, IOS and other inflammatory indices—and we found that HFA-BDP is better than FP [in its effects on] alveolar NO, diffusion capacity and airway sensitivity."

Summary

Results from rigorously conducted retrospective studies reflective of real-world clinical settings indicate that at a lower dose, HFA-BDP controls asthma and reduces exacerbation rate as well as FP and reduces use of SABA. The addition of HFA-BDP to an existing asthma treatment regimen that included an ICS/LABA combination product was associated with improvement in FEV_1 and clinical symptoms. It was also found to have more beneficial effects on measures of inflammation in small airways than FP in a prospective study. □

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