Original Article

Abrupt withdrawal of inhaled corticosteroids does not result in spirometric deterioration in chronic obstructive pulmonary disease: Effect of phenotyping?

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Abstract:

BACKGROUND AND OBJECTIVE: Some studies show a decline of FEV_1 only one month after withdrawal of inhaled corticosteroids (ICS), while others show no decline. We speculate that the presence of an asthma phenotype in the Chronic Obstructive Pulmonary Disease (COPD) population, and that its exclusion may result in no spirometric deterioration.

METHODS: We performed a prospective clinical observation study on 32 patients who fulfilled the Global Initiative for Chronic Obstructive lung disease definition of COPD (Grade II-IV). They were divided into two phenotypic groups. 1. Irreversible asthma (A and B) (*n* = 13): A. Asthma: Bronchial biopsy shows diffuse thickening of basement membrane (≥ 6.6 μm). B. Airflow limitation (AFL) likely to be asthma: KCO > 80% predicted if the patient refused biopsy. 2. COPD (A and B) (*n* = 19): A. COPD: hypercapneic respiratory failure with raised bicarbonate, panlobular emphysema with multiple bullas, or bronchial biopsy showing squamous metaplasia and epithelial/subepithelial inflammation without thickening of the basement membrane. B. AFL likely to be COPD: KCO < 80% predicted.

RESULTS: The asthma phenotype was significantly younger, had a strong association with hypertrophy of nasal turbinates, and registered a significant improvement of FEV_1 (350 ml) *vs* a decline of - 26.5 ml in the COPD phenotype following therapy with budesonide/formoterol for one year. Withdrawal of budesonide for 4 weeks in the COPD phenotype resulted in FEV_1 + 1.33% (SD ± 5.71) and FVC + 1.24% (SD ± 5.32); a change of <12% in all patients.

CONCLUSIONS: We recorded no spirometric deterioration after exclusion of the asthma phenotype from a COPD group.

Key words:

Asthma, COPD, radiology and other imaging, respiratory function tests

The role of inhaled corticosteroids (ICS) in Chronic Obstructive Pulmonary Disease (COPD) management is still controversial. Although ICS are universally accepted to reduce COPD exacerbations by about 25%, their efficacy in other areas is widely debated.[1-7] The balance seem to be tipping in their favor; many studies show a significant rise of FEV_1 with ICS, compared with placebo.[8-11] On the other hand, a decline in FEV_1 with ICS withdrawal (after only one month) has also been reported.[12] This has deterred many of our colleagues from withdrawing ICS, even in patients who do not qualify for such treatment according to the Global Initiative for Chronic Lung Disease (GOLD) criteria (frequent exacerbations and FEV_1 < 50% predicted).[13] Studies on the effects of withdrawing ICS on spirometric deterioration yield conflicting results.[12,14-16]

We hypothesize that ICS withdrawal would not produce significant spirometric deterioration provided that by careful selection, patients with irreversible asthma are removed from the "COPD" group. Studies show that 20-48% of "COPD" patients have features characteristic of irreversible asthma.[17-19] Smoking is an important risk factor for both irreversible asthma and COPD.[20] Moreover, the two conditions have been known to be concomitantly, or alternately, ascribed to the same patient.[21] Phenotyping is documented to predict the response to corticosteroids in COPD.[17,19,22-24] Several authors have recommended targeting treatment to the COPD phenotype.[25,26]

In our practice, ICS are routinely withdrawn in the COPD phenotype in the spring and summer months when the risk of exacerbations is at its

lowest. We decided to study the effect of the withdrawal on spirometry.

Methods

Patient selection and diagnostic criteria

This is a prospective clinical observation study conducted between April and May 2009 at King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia, and approved by the King Saud University's Internal Review Board for ethics approval. All patients attending the Respiratory Medicine clinics in the six months prior to the study were screened. Subjects were smokers (≥ 10 pack/year) with airflow limitation (AFL) (FEV_1 < 80% predicted, FEV_1/FVC < 70%) that was persistent despite budesonide/formoterol treatment (320 µcg budesonide/9 µcg formoterol bid for at least 3 weeks). Patients in this group who fulfilled the Global Initiative for Chronic Obstructive lung disease diagnostic criteria for COPD were labeled as undiagnosed AFL, and further subdivided into irreversible asthma or COPD phenotypes. Irreversible asthma was diagnosed if the bronchial biopsy showed uniform thickening of the basement membrane of 6.6 µm or more.[27] The diagnosis was registered as AFL likely to be irreversible asthma, in any patient who refused biopsy and had normal diffusing capacity for carbon monoxide coefficient (KCO ³ 80 % predicted).

COPD was diagnosed in the presence of any of the following: 1) Chronic hypercapneic respiratory failure at least one month outside exacerbations; defined as $PaO_2 \leq 60$ mm Hg, $PaCO_2 > 45$ mm Hg, and serum bicarbonate > 28 m mol/l; 2) Panlobular emphysema with bullas larger than 2 cm observed with high-resolution computerized tomography (HRCT). Panlobular emphysema was defined as areas of low attenuation without a well-defined wall and associated with vascular and septal disruption; 3) Squamous metaplasia with epithelial/subepithelial inflammation and a reticular basement membrane of 6.0 µm or less, observed with bronchial biopsy.[27] AFL likely to be COPD was diagnosed if the KCO was less than 80% predicted. The rationale for this classification is described in more detail in the discussion, and elsewhere.[19]

It was routine practice to use HRCT, arterial blood gases, fiberoptic biopsy of the 3rd order bronchus, and diffusion studies, as part of the diagnostic work-up of AFL in smokers of more than 10 pack/year and who fulfilled the GOLD definition of COPD.[19] We had four diagnostic slots: irreversible asthma or AFL likely to be asthma (grouped as the irreversible asthma phenotype), and COPD or AFL likely to be COPD (grouped as the COPD phenotype). ICS are routinely withdrawn in the COPD phenotype in the spring and summer months (April-September) when the risk of exacerbations is at its lowest. The data from this study was published as an abstract in the Gulf Thoracic 2011, the annual meeting of the Saudi Thoracic Society.[28]

Statistical analysis

The data were analyzed using the statistical Software Package (SPSS pc + version 13.0; SPSS Inc, USA). The Mann-Whitney U-Test was used to compare the median values of skewed continuous variables. The Chi-square and Fisher's exact test were used to observe an association between categorical study and outcome variables. A *P* value < 0.05 was considered statistically significant.

Results

There were a total of 32 patients with undiagnosed AFL. Of these, 13 were of the irreversible asthma phenotype: eight with asthma and five with AFL likely to be asthma. The remaining 19 were of the COPD phenotype based on the following: six had panlobular emphysema with bullas, four patients had hypercapneic respiratory failure, one patient had both, and a positive bronchial biopsy in five. Three patients had AFL likely to be COPD. All were male patients. Table 1 gives the characteristics of both phenotypes and shows significant differences. Patients in the irreversible asthma phenotype were younger, had earlier onset of wheeze and dyspnea (45 *vs* 59 years), and were more likely to suffer from allergic rhinitis and hypertrophy of nasal turbinates. They also achieved a mean rise of FEV1 of 350 ml with budesonide/formoterol, *vs* a decline of -26.5 ml in the COPD phenotype.

Four weeks after budesonide withdrawal in the COPD phenotype group, changes in FEV1 and FVC were 1.33% (±5.71) and 1.24% (±5.32), respectively. The change was <12% and 200 ml in all patients [Figure 1].

Discussion

We showed no spirometric deterioration following budesonide withdrawal in a small group of COPD patients where the asthma phenotype was excluded (based on bronchial histology and normal coefficient of carbon monoxide diffusion, KCO). We also show that phenotyping based on CT scanning and bronchial biopsy can be applied in routine clinical practice to predict responses to withdrawal of ICS. Phenotyping has been described as the "future of COPD."[29] There is mounting evidence that COPD phenotypes differ in their physiology and response to B_2-agonists and corticosteroids. Using HRCT scanning, Fujimoto *et al.* classified COPD into the following three phenotypes: 1) absent emphysema regardless of bronchial wall thickening (phenotype A), 2) emphysema with bronchial wall thickening (phenotype M), and 3) predominantly emphysema (phenotype E).[30] Phenotype A is associated with normal diffusing capacity for carbon monoxide (DL_{CO}) and is significantly reversible with β_2 agonists. Phenotype M is also

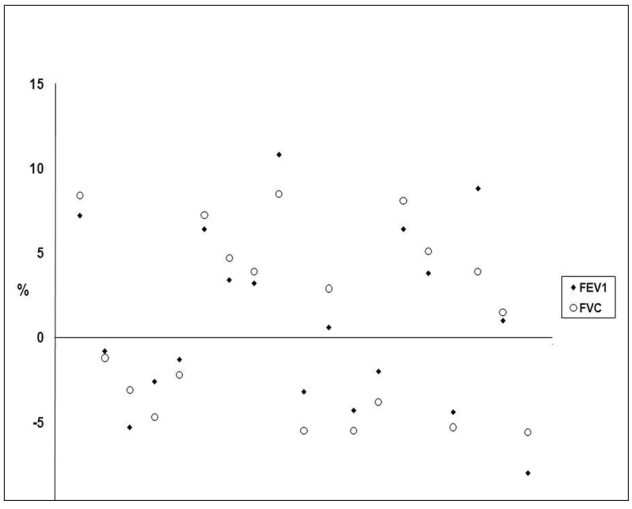

Figure 1: Change of FEV1 and FVC after withdrawal of inhaled corticosteroids

Table 1: Characteristics of irreversible asthma and COPD phenotypes

Final diagnosis	Irreversible asthma phenotype (*n* = 13) median (Range)	COPD phenotype (*n* = 19) median (Range)	*P* value
Age*	55 (42 to 61)	67.5 (49 to 70)	0.001 (S)
Smoking			
11-19 (pack/year)	1 (7.7%)	0 (0%)	
20-29 (pack/year)	0 (0%)	0 (0%)	
30-39 (pack/year)	1 (7.7%)	0 (0%)	
40-49 (pack/year)	3 (23.1%)	0 (0%)	
50 or more	8 (61.5%)	19 (100%)	
Age at onset of chronic cough (year)*	40 (22 to 57)	49.5 (30 to 60)	0.10
Age at onset of chronic expectoration (year)*	40 (24 to 57)	49.5 (30 to 60)	0.09
Age at onset of wheeze (year)*	45 (9 to 57)	54 (40 to 69)	0.003 (S)
Age at onset of exercise intolerance/dyspnea (year)*	45 (9 to 57)	59 (40 to 64)	0.009 (S)
History of allergic rhinitis†	11 (84.6%)	4 (21.1%)	0.0015 (S)
Hypertrophy of nasal turbinates†	12 (92.3%)	5 (26.3%)	0.0009 (S)
Symptoms triggered by external factors‡	11 (84.6%)	11 (57.9%)	0.11
Severity by GOLD Criteria: ‡			
Stage II (Moderate) FEV1 <80%-50%	11	13	0.271
Stage III or IV (severe or very severe) FEV1 <50%	2	6	
Change of FEV1** at the end of 1 year (ml)	350 (-200 to 600)	-26.5 (-120 to 91)	<0.0001 (S)

*Mann-Whitney U-test. †Chi-Square Test. ‡Fisher's exact test. **Forced expiratory volume in the first second. COPD - Chronic Obstructive Pulmonary Disease; GOLD - Global Initiative for Chronic Lung Disease

reversible but has low DL_{CO}.[30] Phenotype E has a low DL_{CO} and no significant reversibility.[30] Fujimoto *et al.* speculated that some patients in phenotype A are asthmatic.[30] Chanez *et al.* showed that 12 of 25 "COPD" patients had significant reversibility with oral prednisolone and bronchial biopsy revealed uniform thickening of the basement membrane in those 12 patients, compatible with irreversible asthma.[17] In 2010, Lee *et al.* measured the CT emphysema score in the lung (areas of attenuation below -950 Hounsfield units at full inspiration) and found a correlation with low DLCO and lack of bronchodilator response, or improvement of dyspnea score following three months of combined LABA/ICS therapy.[24] Other studies report improved FEV_1 and shuttle distance in response to ICS or prednisolone only in COPD patients with a high sputum eosinophil count.[22,23] Barnes and others speculate that eosinophilic cases represent an asthmatic component of the COPD syndrome, or concomitant asthma and COPD.[7] If phenotyping with HRCT, bronchial biopsy, or sputum cytology had not been applied in these studies, the patients would have been labeled as "COPD" and prednisolone and ICS would have shown a bronchodilator effect. A recently released Consensus Document in Spain recommends major and minor criteria for diagnosing the asthma phenotype in the COPD population.[31]

We found that a physiological and anatomical phenotyping based on arterial blood gases, HRCT, and bronchial biopsy in addition to KCO is a simple and reliable means of differentiating asthma and COPD and predicting the response to ICS and yearly decline of FEV_1.[19] We currently use this phenotyping approach in smokers who remain obstructive despite treatment with formoterol (9 µcg) and budesonide (360 µg bid), administered for at least three weeks. In this study, COPD was diagnosed by the presence of chronic hypercapneic respiratory failure, panlobular emphysema with bullas, or bronchial biopsy showing COPD changes (as described in the methods section). Large studies on patients receiving long-term oxygen for chronic respiratory failure included no asthmatics.[32,33] We found no reports of chronic hypercapnia with raised bicarbonate in stable asthma outside exacerbations. We found a report where some elderly subjects with irreversible asthma (average FEV_1 55 ± 0.5% predicted) required home oxygen therapy.[34] Even in that extreme group with marked obstruction, the alveolar-arterial gradient for oxygen was only 22.1 ± 1.6 mm Hg, and PaO_2 was 76.9 ± 1.7 mm Hg. It is not mentioned whether home oxygen was used intermittently or asthma exacerbations or continuously.[34] Although mild centrilobular and paraseptal emphysematous changes are occasionally seen in asthma, panlobular emphysema has never been described.[35] Irreversible asthma is diagnosed exclusively by bronchial biopsy where diffuse thickening of the basement membrane to 6.6 µm or more is observed. Early studies stated that thickening of the basement membrane could not differentiate asthma and COPD,[36,37] but these studies were conducted on patients with reversible asthma and normal FEV_1.[37] In Fabbri's landmark study on the histological differentiation of asthma and COPD, they used patients with FEV_1 of about 60% predicted in both groups and showed no overlap in the thickness of the basement membrane between the groups (6.6-9.7 µm *vs* 4.2-6.2 µm).[27] In Fabbri's study, and others, the thickness of the basement membrane was a predictor of response to oral prednisolone and ICS.[17,19,27] In addition, the thickness of the basement membrane (and other histological features) was strongly associated with atopic features such as a history of allergic rhinitis and hypertrophy of nasal turbinates. [19] Patients with a KCO <80% predicted and who refused bronchial biopsy were given the diagnostic label of undiagnosed AFL likely to be COPD. Normal or high diffusion capacity is consistently observed in asthma, even when it is severe or irreversible, unless there is concomitant bronchiectasis where DLCO may be reduced.[38,39] In Fabbri's study, the mean carbon monoxide diffusion capacity was 65.4 and 85% predicted in irreversible asthma and COPD, respectively, and the mean KCO was 60% and 82.9%, respectively. [27] Al-Kassimi *et al.* recently

reported total concurrence between bronchial histology and KCO in both irreversible asthma and COPD.[19] Earlier studies produced conflicting results on the sensitivity and specificity of diffusion capacity for distinguishing asthma and COPD but no phenotyping was done. In Fujimoto's stratification by CT scan, the DLCO of E and M phenotypes were 49.3 ± 2.1 and 61.6 ± 2.8% of predicted, respectively.[30]

The 19 patients in this study, who were strictly selected from a total of 32 "COPD" patients where irreversible asthma phenotypes were excluded, displayed no decline of FEV_1 or FVC, four weeks after withdrawal of ICS. Previous studies on the effect of withdrawal of ICS on FEV_1 yielded conflicting results. In a small crossover study on 24 patients (only 15 completed the study), FEV_1 declined significantly on withdrawal of beclomethasone, but the six-minute walk test was unchanged.[16] Their results support the possibility that asthmatic patients were inadvertently included: some patients had normal diffusion capacity, and the decline of FEV_1 occurred in some but not all patients.[16] Another study reported a significant decline of FEV_1 one month after withdrawal of fluticasone.[12] However, the decline of FEV_1 was modest at 4.1% (95% CI, 1.6-6.6) even at twelve months.[12] The study also used 10% reversibility upon salbutamol inhalation as a criterion for excluding asthma and single reversibility tests have been shown to be unable to distinguish irreversible asthma and COPD.[40] On the other hand, the COPE study failed to detect any significant decline of FEV_1, 6-minute walk test, or Borg Scale of breathlessness following withdrawal of ICS.[15] Similarly, a study conducted in primary care in the U.K. found no significant deterioration of FEV_1 or the St. George's respiratory questionnaire.[14]

The claims that ICS, either after induction or withdrawal, have a large effect on FEV_1 raise the following objections:

1. In COPD, there is reduced activity of histone deacetylation, which is the main mechanism of suppression of inflammatory genes by corticosteroids.[41,42] This persists even after cessation of smoking.[41] ICS were found to have no effect on inflammatory cells or markers in patients with COPD, or *in vitro* at a cellular level.[43-47]
2. Some of the large trials of ICS in COPD used two sets of patients: 1) a "reversible," group who improved their average FEV_1 by 29% post 400 mcg salbutamol, and 2) an "irreversible" group, with only 8% salbutamol reversibility.[10] El-Kassimi suggested in 2004 that these studies on "COPD" had inadvertently included patients with asthma, which explained the bronchodilator effect of ICS.[48] The suggestion was based, not only on the above figures of salbutamol reversibility, but also on the fact that patients with a previous history of asthma were included.[10]

Our study has the limitation of a small number of patients. This is related to the fact that the large-scale epidemic of smoking is a recent phenomenon in Saudi Arabia. A further limitation is the short duration of ICS withdrawal. This limitation may be mitigated, however, by the fact that previous studies reported spirometric deterioration only one month after ICS withdrawal.[12] Lastly, this was not a drug trial where we could also have withdrawn budesonide in the irreversible asthma phenotype patients. As seen from Table 1, the irreversible asthma phenotype achieved a 350 ml rise of FEV_1 after one year of budesonide/formoterol therapy and probably would have experienced significant deterioration upon ICS withdrawal. The previous studies on ICS withdrawal did not also use an asthmatic control group. The Spanish Consensus Document advises caution with abrupt withdrawal of ICS in the asthma phenotype.[31]

In conclusion, in a small population of COPD sufferers, where the irreversible asthma phenotype (+ve bronchial biopsy or normal KCO) was excluded, there was no significant drop of FEV_1 or FVC four weeks after withdrawal of budesonide.

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