ORIGINAL RESEARCH LETTER

# Inhaled beclomethasone/formoterol in idiopathic pulmonary fibrosis: a randomised controlled exploratory study

*To the Editor:*

We hypothesise that inflammation plays a role in idiopathic pulmonary fibrosis (IPF) and that the harm associated with corticosteroid-containing regimens in IPF may relate to local beneficial effects being counterbalanced by deleterious systemic effects [1, 2]. Topical lung delivery could improve the poise between risk and benefit.

Inhaled corticosteroids (ICS) are widely used in airway diseases to target inflammation, often in combination with long-acting $\beta_2$-adrenoceptor agonists (LABA). Human lung fibroblasts express $\beta_2$-adrenoceptors, and agonist-induced downregulation of collagen synthesis and myofibroblast differentiation has been demonstrated *in vitro* [3]. Inhibition of profibrotic mediator release in response to transforming growth factor-β1 has also been demonstrated [4]. Thus, there is a pharmacological rationale to study ICS/LABA combinations in IPF.

Platelets provide a potential link between inflammation and fibrosis, and have been shown to accumulate and correlate with collagen deposition in the lungs of animals with bleomycin induced lung injury [5]. We have demonstrated increased platelet–monocyte interactions [6] and propensity for platelet activation in response to physiological agonists in IPF patients [7]. A physiological consequence of platelet activation is thrombosis, and the association between IPF and thrombotic vascular diseases is well documented [8]. We propose that markers of platelet activation reflect a pathological process in IPF and may have utility as a biomarker.

We report the findings of an exploratory, double-blind, placebo-controlled, randomised, crossover trial of "ultrafine" inhaled beclomethasone/formoterol in IPF. Patients attending a single tertiary centre were randomised to receive either 4 weeks' treatment with a beclomethasone/formoterol (Fostair; Chiesi, Parma, Italy) 100/6 µg hydrofluoroalkane pressurised metered-dose inhaler, two puffs twice per day, followed by matched placebo or *vice versa* in a 2×2 crossover design with a 4-week washout period. Patients were eligible for inclusion if they were aged 40–85 years, had an IPF diagnosis made by a multidisciplinary team in accordance with international consensus criteria and had a forced vital capacity (FVC) of 50–110% predicted, carbon monoxide transfer factor ⩾30% predicted and oxygen saturations ⩾89% while breathing room air. Potential participants were excluded if they had a secondary cause for their pulmonary fibrosis, were current smokers and/or they had used any of the following medications in the past 3 months: ICS, LABA, pirfenidone, oral corticosteroids or antiplatelet therapy that may have altered assessment of study end-points (*e.g.* clopidogrel, prasugrel and dipyridamole). The study was approved by the regional research ethics committee (Local Research Ethics Coordinator reference 14/YH/0053).

We chose change in platelet activation from baseline as the primary outcome of this exploratory study. Platelet–monocyte aggregate (PMA) formation, P-selectin expression and fibrinogen binding were evaluated using whole-blood flow cytometry when unstimulated and following stimulation with ADP [7].

Secondary outcome measures recorded at baseline and the end of each treatment period included lung function (forced expiratory volume in 1 s ($FEV_1$), FVC and forced expiratory fraction at 25–75% of FVC ($FEF_{25–75\%}$)), quality of life (the Kings Brief Interstitial Lung Disease (K-BILD) questionnaire), exercise

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**Cite this article as:** Wright CE, Fraser SD, Brindle K, *et al.* Inhaled beclomethasone/formoterol in idiopathic pulmonary fibrosis: a randomised controlled exploratory study. *ERJ Open Res* 2017; 3: 00100-2017 [https://doi.org/10.1183/23120541.00100-2017].

capacity (6-min walk distance (6MWD)), physical activity (mean step count over 7 days) and airway inflammation (exhaled nitric oxide fraction ($F_{ENO}$) and sputum differential cell count).

Data are presented as mean±SD. Differences were assessed between groups and before and after treatment using Student's t-tests. A two-tailed $p<0.05$ was considered significant. Platelet activation markers were compared using the mean area under the concentration–response curve (AUC). Changes in AUC were compared using ANOVA and Tukey's *post hoc* test.

20 patients were screened, with 17 proceeding to randomisation and completing the study (males/females 11/6; age 71.1±8.7 years; 10 ex-smokers, six never-smokers and one with unknown smoking history; baseline $FEV_1$ 2.10±0.60 L (89.9±15.3% predicted), FVC 2.64±0.79 L (86.2±17.4% predicted), $FEV_1$/FVC 82.4%±5.6% and $FEF_{25–75\%}$ 2.4±0.98 L (90±31.3% predicted)). Participants had IPF diagnosed by multidisciplinary assessment according to international criteria and no participants had evidence of airflow obstruction at study entry.

Beclomethasone/formoterol significantly reduced platelet P-selectin expression from baseline (AUC: baseline, 283.2±123.8; beclomethasone/formoterol, 196.9±72; $p<0.05$). PMA formation and fibrinogen binding showed trends to reduction compared to baseline. Compared to placebo, there were trends towards reduced platelet reactivity (P-selectin: AUC 196.9±72 following beclomethasone/formoterol and 224.3±79.9 following placebo; PMA: 330.2±180.6 and 381.8±224.3; fibrinogen: 685.7±188.3 and 769.1±154.5, respectively). The greatest differences were observed following stimulation with higher concentrations of ADP (figure 1).

Beclomethasone/formoterol improved $FEV_1$ (+0.07 L *versus* placebo, $p<0.05$) and $FEF_{25–75\%}$ (+0.19 L *versus* placebo, $p<0.05$) (figure 1). Sputum eosinophil counts decreased from 5.7±5.6% at baseline to 2.2±2.5% following placebo (nonsignificant) and 1.2±1.2% following beclomethasone/formoterol ($p<0.05$ compared to baseline, nonsignificant compared to placebo). No changes were observed in FVC, K-BILD, 6MWD, mean step count or $F_{ENO}$.

The findings of this exploratory study demonstrate the potential for this inhaled combination therapy to tackle various aspects of this complex and poorly understood condition. ICS therapy targets the inflammatory process whereas the LABA contributes to bronchodilation and has activity on platelet activation.

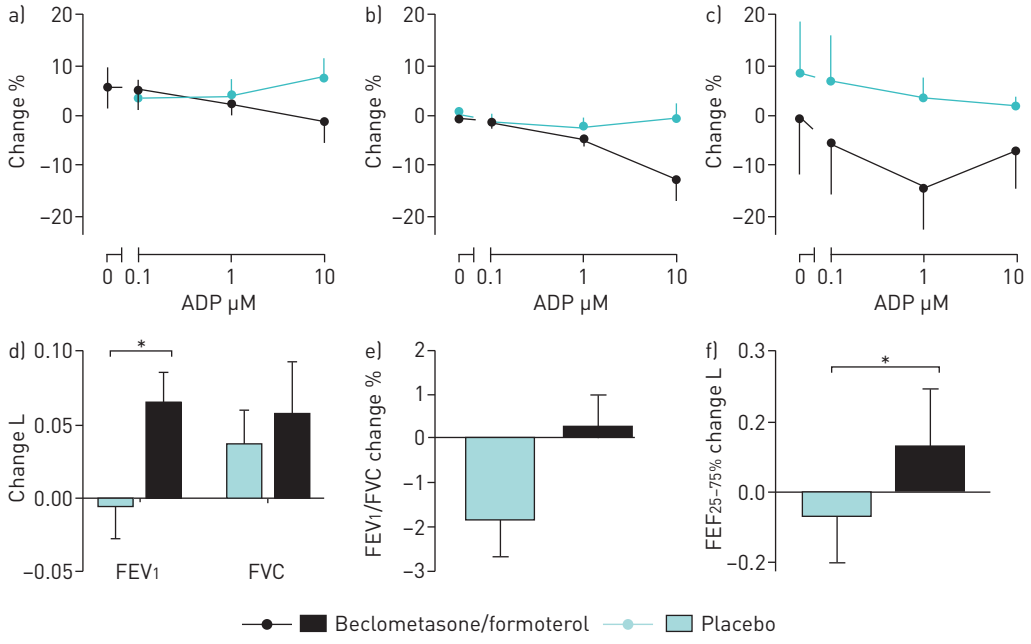


FIGURE 1 Change from baseline following beclomethasone/formoterol and placebo in a) platelet–monocyte aggregate formation, b) P-selectin expression and c) platelet fibrinogen expression when unstimulated and following stimulation with ADP 0.1–10 µM. Change from baseline in d) forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC), e) forced expiratory ratio and f) forced expiratory fraction at 25–75% of FVC ($FEF_{25–75\%}$) following treatment with beclomethasone/formoterol *versus* placebo. Data are presented a mean±SEM. *: $p<0.05$.

Platelet activation leads to proinflammatory and profibrotic mediator release. Therefore, the increased platelet reactivity observed in IPF patients has potential pathophysiological consequences. Despite higher than expected variability of the platelet assays and our small sample size limiting our ability to demonstrate statistically significant change, consistent trends towards reduced platelet reactivity were observed across the range of markers in response to treatment. Beclomethasone/formoterol may affect platelet reactivity directly through activity on platelet $\beta_2$-adrenoceptors [9] and potentially glucocorticoid receptors [10] (the presence of glucocorticoid receptors on platelets remains contentious), or indirectly though reduction of inflammation and fibrosis.

By using inhaled beclomethasone/formoterol with extra-fine particles (1.5 µm), we aimed to achieve delivery of the drug to peripheral airways [11] where abnormalities have been demonstrated in IPF lung explants [12]. It is interesting that we observed improvements in $FEV_1$ and $FEF_{25–75\%}$ from baseline compared to placebo, with the latter measure often considered to reflect small airways. This supports the presence of a potentially modifiable pathology in the small airways of these patients who, at study entry, had no physiological evidence of airflow obstruction.

The sputum eosinophil data support previous demonstration of sputum eosinophilia in IPF patients [13]. The observed reduction in sputum eosinophilia during the study was most marked following beclomethasone/formoterol but also occurred, to a lesser extent, following placebo. The small proportion of patients that were able to provide sputum samples at every study time-point limits the generalisability of this finding but it supports the hypothesis that there is modifiable inflammation in IPF airways.

We excluded patients with demonstrable airflow obstruction and no participants in this study had obstructive spirometry ($FEV_1/FVC$ ratio <0.7). Although we cannot rule out nascent obstructive airway disease, we believe our patients are typical of those presenting to specialist interstitial lung disease clinics and suggest that the small airways may represent a neglected therapeutic target in IPF.

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Received: Aug 14 2017 | Accepted after revision: Oct 20 2017

This trial is registered at eudract.ema.europa.eu with identifer number 2013-004404-19

Support statement: This research was funded by Chiesi Ltd. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflicts of interest: Disclosures can be found alongside this article at openres.ersjournals.com

Acknowledgements: A.H. Morice, S.P. Hart and M.G. Crooks conceived and designed the study; K. Brindle, C.E. Wright and S.D. Fraser acquired the data during the study, and S.D. Fraser, C.E. Wright, A.H. Morice, S.P. Hart, M.G. Crooks analysed and interpreted those data; C.E. Wright, A.H. Morice, S.P. Hart and M.G. Crooks drafted the manuscript, and all authors critically reviewed it and approved the submitted version.

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