

Bronchodilatory Effect of the PPAR- γ Agonist Rosiglitazone in Smokers With Asthma

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Smokers with asthma show a reduced response to inhaled corticosteroids. We hypothesized that a peroxisome proliferator-activated receptor- γ (PPAR- γ) agonist would be superior for the clinical treatment of these asthma patients. Forty-six smokers with asthma were randomized to inhaled beclometasone dipropionate (200 μ g per day) or rosiglitazone (8 mg per day) for 4 weeks. Rosiglitazone produced improvements in lung function (forced expiratory volume in 1 s (FEV₁) = 183 ml, $P = 0.051$; forced expiratory flow between 25 and 75% of the forced vital capacity (FEF₂₅₋₇₅) = 0.24 l/s, $P = 0.030$) as compared with inhaled beclometasone dipropionate. Further trials using PPAR- γ agonists in steroid-resistant airway disease are indicated.

Inhaled corticosteroids are recommended as the first line of treatment in patients with chronic persistent asthma.¹ Smokers with asthma, however, exhibit an impaired response to both inhaled and oral corticosteroids,²⁻⁵ possibly because of noneosinophilic airway inflammation, impaired glucocorticoid receptor function, and/or reduced histone deacetylase activity.⁶ Cigarette smoking in asthma patients is also associated with an accelerated decline in lung function,⁷ increase in the number of emergency department visits for asthma (with associated costs)^{7,8} and increase in severity of symptoms, as compared with nonsmoking asthmatic patients.⁹ The prevalence of smoking in subjects with asthma reflects the prevalence in the general population, and therefore smokers with asthma constitute a large group of patients with poorly controlled disease.¹⁰ Smoking cessation is an effective therapy in this group,¹¹ but because sustained quitting rates are low, additional or alternative therapies are needed for individuals with asthma who continue to smoke.

The glucocorticoid receptor is a member of the nuclear hormone receptor family, which includes the peroxisome proliferator-activated receptor- γ (PPAR- γ). PPAR- γ agonists exert anti-inflammatory effects on multiple inflammatory cell

subtypes *in vitro* and reduce inflammation in animal models of asthma and neutrophilic airways disease.¹² On the basis of this evidence, we hypothesized that the PPAR- γ agonist rosiglitazone would have anti-inflammatory activity that would be of benefit in smokers with asthma. Therefore, we undertook an exploratory clinical trial to examine the effect of rosiglitazone on lung function, Asthma Control Questionnaire (ACQ) score, and inflammatory end points in a group of smokers with asthma.

RESULTS

A total of 3,895 subjects with asthma were invited to participate in the study between August 2005 and May 2007, of whom 294 gave positive responses. Following screening through telephone calls, visits were arranged for 187 subjects. After a run-in period involving weaning from inhaled corticosteroids and assessment of bronchodilator reversibility, 91 subjects met the criteria for randomization (see Methods for further details). The trial contained four treatment arms, and subjects were randomly allocated to the various treatments. Forty-five subjects were randomized to other treatments, which are not discussed in this article.¹³ The other 46 subjects were randomized equally to rosiglitazone and inhaled beclometasone dipropionate. The demographic, clinical (including previous inhaled corticosteroid and long-acting β_2 -agonist use), and inflammatory baseline characteristics of the recruited subjects in each group were well matched (Table 1). All the end points presented are the changes relative to the response in the group assigned to inhaled corticosteroids.

Lung function

At 2 weeks, rosiglitazone demonstrated a borderline improvement in prebronchodilator forced expiratory volume in 1 s (FEV₁) (164 ml, 95% confidence interval (CI), -1 to 329, $P = 0.051$) (Figure 1a and Table 2), a significant improvement in prebronchodilator peak expiratory flow (32.7 l/min, 95% CI

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Table 1 Baseline demographics and induced sputum results

Characteristic	Inhaled beclometasone	Rosiglitazone
No. of patients	23	23
Age (years)	42 (36, 53)	41 (33, 54)
Female (% of total)	61	57
BMI (kg/m ²) (mean (range))	25.5 (18.4, 34.2)	26.1 (19.5, 38.6)
Pack-years	24 (15, 30)	21 (13, 40)
Duration of asthma (years)	16 (8, 31)	18 (6, 29)
Inhaled corticosteroid use at screening (% of subjects)	65	83
Inhaled corticosteroid dose at screening (dose (beclometasone equivalent) µg)	800 (400, 800)	800 (400, 800)
LABA use at screening (%)	26	30
Specific IgE antibody positive (%)	61	78
Total IgE level (IU/ml)	87 (34, 396)	239 (49, 488)
Pre-BD FEV ₁ (% predicted)	75 (72, 89)	70 (60, 89)
Pre-BD PEF (l/min)	394 (109)	361 (109)
Pre-BD FEF ₂₅₋₇₅ (l/s)	1.89 (0.88)	1.71 (0.82)
Reversibility (FEV ₁ % improvement)	16 (13, 20)	16 (13, 26)
ACQ (0–6) (mean (SD))	1.8 (0.9)	1.9 (0.7)
Sputum total cell count (10 ⁶)	4.3 (2.6, 7.3)	4.7 (2.4, 9.9)
Eosinophils (%)	0.9 (0.3–1.6)	1.1 (0.5–3.0)
Eosinophils (absolute count (10 ⁴ cells))	2.1 (0.8, 5.8)	5.1 (1.5, 17.9)
Neutrophils (%)	25.5 (9.6–44.6)	28.8 (13.1–46.2)
Neutrophils (absolute count (10 ⁴ cells))	122.7 (25, 188)	150.3 (27, 492)
Macrophages (%)	52.8 (32.0–64.4)	48.0 (26.1–64.1)
Macrophages (absolute count (10 ⁴ cells))	184.2 (96, 437)	185.8 (105, 355)
Lymphocytes (%)	1.3 (0.6, 2.6)	1.4 (0.7, 2.0)
Lymphocytes (absolute count (10 ⁴ cells))	4.9 (2.3, 11.2)	8.0 (2.1, 13.5)
Bronchial epithelial cells (%)	10.5 (8.3, 15.4)	11.0 (6.7, 18.8)
Bronchial epithelial cells (absolute count (10 ⁴ cells))	40.7 (20.5, 99.4)	49.6 (28.4, 110.6)

Data presented as median (interquartile range) unless stated otherwise.

95% CI; 95% confidence interval; ACQ, Asthma Control Questionnaire score (range, 0–6, with higher scores indicating worse asthma control); BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FEF₂₅₋₇₅, forced expiratory flow between 25 and 75% of the forced vital capacity; IgE, immunoglobulin E; IU, international units; LABA, long-acting β₂-agonist; PEF, peak expiratory flow; pre-BD, prebronchodilator.

5.7–59.7, $P = 0.018$), and significant improvement in both forced expiratory flow between 25 and 75% of the forced vital capacity (FEF₂₅₋₇₅) (0.36 l/s, 95% CI, 0.09–0.63, $P = 0.010$) (Figure 1b) and FEF₇₅ (0.24 l/s, 95% CI, 0.09–0.39, $P = 0.002$). After 4 weeks, the group treated with rosiglitazone again demonstrated a borderline improvement in prebronchodilator FEV₁ (183 ml 95% CI –1.0 to 367.0, $P = 0.051$) (Figure 1a and Table 2) and a significant improvement in FEF₂₅₋₇₅ (0.24 l/s, 95% CI, 0.03–0.46, $P = 0.030$) (Figure 1b and Table 2). With respect to other measurements of lung function, there was no difference between the two groups.

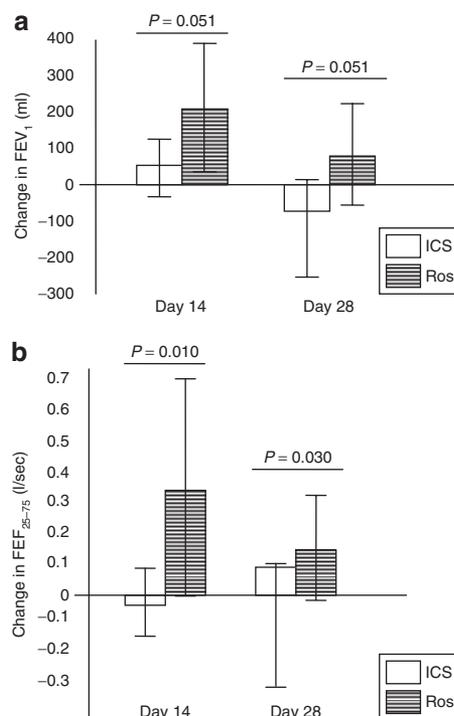


Figure 1 Comparison of treatment responses at 14 and 28 days. (a) Change in forced expiratory volume in 1 s (FEV₁) (ml) at 14 and 28 days. (b) Change in forced expiratory volume in 1 s (FEF₂₅₋₇₅) (l/s) at 14 and 28 days. The changes presented are mean group changes from randomization to 14 and 28 days of treatment (paired t-test; error bars represent 95% confidence intervals). P values were derived by comparing the relative changes in the two treatment arms, using analysis of covariance. ICS, inhaled corticosteroid (beclometasone dipropionate); Rosi, rosiglitazone.

ACQ score

When changes in ACQ scores were compared (Table 2), there was no difference between the rosiglitazone group and the one on inhaled beclometasone dipropionate.

Sputum samples

Induced sputum cytology. No relative differences in sputum cell proportions were observed between the two treatment arms (Table 2).

Sputum supernatant. A borderline reduction in sputum interleukin-8 was observed in the group treated with rosiglitazone (–534.1 pg/ml, 95% CI, –1,844.4 to 36.5, $P = 0.068$) relative to the group on inhaled beclometasone dipropionate (Table 2).

Compliance

Eighty-five percent of the subjects who completed the study achieved >80% compliance with therapy.

Adverse events

No serious adverse events occurred in subjects in either of the treatment arms during the trial. There were two withdrawals due to adverse events. One occurred in the rosiglitazone group (allergic reaction, periorbital edema) and one in the inhaled beclometasone dipropionate group (diarrhea and vomiting).

Table 2 Predefined and exploratory end point changes

End point	Change by 14 days	Change by 28 days
Δ Pre-BD FEV ₁ (ml (95% CI))	164 [†] (−1, 329)	183 [†] (−1, 367)
Δ Pre-BD FVC (ml (95% CI))	45 (−114, 204)	156 (−42, 354)
Δ Pre-BD PEF (l/min (95% CI))	32* (5, 59)	23 (−6, 53)
Δ Pre-BD FEF _{25–75} (l/s (95% CI))	0.36* (0.09, 0.63)	0.24* (0.03, 0.46)
Δ Pre-BD FEF ₇₅ (l/s (95% CI))	0.24* (0.09, 0.39)	0.11 (−0.01, 0.23)
Δ ACQ score (Δ (95% CI))		−0.07 (−0.52, 0.38)
Δ Sputum total cell count (10 ⁶)		1.3 (−2.1, 4.7)
Δ Eosinophils (%)		0.1 (−1.0, 1.3)
Δ Eosinophils (absolute count (10 ⁴ cells))		1.42 (−4.71, 6.05)
Δ Neutrophils (%)		4.5 (−16.5, 26.5)
Δ Neutrophils (absolute count (10 ⁴ cells))		32.9 (−120.4, 201.1)
Δ Macrophages (%)		3.4 (−13.3, 16.8)
Δ Macrophages (absolute count (10 ⁴ cells))		110.0 (−27.2, 326.8)
Δ Lymphocytes (%)		−0.5 (−1.1, 0.4)
Δ Lymphocytes (absolute count (10 ⁴ cells))		−0.19 (−7.02, 5.22)
Δ Bronchial epithelial cells (%)		−4.7 (−11.3, 2.0)
Δ Bronchial epithelial cells (absolute count (10 ⁴ cells))		5.9 (−65.8, 78.4)
Δ Sputum IL-8 (pg/ml (95% CI))		−534.1 (−1,844.4, 36.5)
Δ Sputum MPO (ng/ml (95% CI))		−91.3 (−335.1, 44.2)

Changes in lung function, Asthma Control Questionnaire (ACQ) score, and induced sputum results following treatment with rosiglitazone (compared to response to treatment with inhaled beclometasone alone). Lung function data and ACQ score differences are difference of adjusted means with adjustment for baseline measurement (analysis of covariance).

Δ, change; 95% CI, 95% confidence interval; FEV₁, forced expiratory volume in 1 s; FEF_{25–75}, forced expiratory flow between 25 and 75% of the forced vital capacity; FVC, forced vital capacity; IL-8, interleukin-8; MPO, myeloperoxidase; PEF, peak expiratory flow; pre-BD, prebronchodilator.

**P* < 0.05, [†]*P* = 0.05.

The frequency of occurrence of headaches was similar in the two the groups (five in the beclometasone dipropionate group and four in the rosiglitazone group). Three subjects in the beclometasone dipropionate group reported pharyngitis.

DISCUSSION

There exists a subpopulation of asthma patients who fail to respond adequately to current therapies.¹⁴ As a result, this group has poorer asthma control and consumes a disproportionate share of health-care budgets. Smokers with asthma are part of this large, difficult-to-treat group. This randomized, controlled, exploratory clinical trial examined the impact of a novel alternative approach using the PPAR-γ agonist rosiglitazone in a group of smokers with mild to moderate asthma.

Treatment with rosiglitazone produced a trend toward improvement in prebronchodilator FEV₁ relative to low-dose inhaled corticosteroids, at both 14 days and 28 days.

This improvement is much larger than the effect seen in previous trials that examined the effect of inhaled corticosteroids in smokers with asthma^{2,3} and was associated with improvements in our predefined secondary lung function end points, suggesting that the FEV₁ improvement is real. The failure to produce a conclusive improvement may be due to an underpowered study design.

The improvement in lung function produced by rosiglitazone was not associated with a reduction in asthma symptoms (as detected by the ACQ score), sputum profile, or supernatant at 28 days. What can explain this? The subjects had relatively mild asthma and did not display sputum eosinophilia or neutrophilia at baseline, and therefore we would not have been able to detect substantial changes in these cells or sputum cytokines. The lack of change in ACQ score is possibly an example of dissociation between change in lung function and ACQ score, as has previously been reported.^{11,15–17}

What is the mechanism by which rosiglitazone produces the improvements that we have detected in lung function? The reason for the poor response to corticosteroids in smokers with asthma is currently unknown. However, one possible reason is that cigarette smoking may induce an oxidative stress-mediated change in the glucocorticoid receptor, resulting in a change in its behavior and efficacy.¹⁸ Recent research has demonstrated that rosiglitazone is able to bind to the glucocorticoid receptor ligand-binding domain and thereby alter gene transcription.¹⁹ Therefore, our results may be a demonstration of an alternative mode of glucocorticoid-receptor activation leading to the detected improvements in lung function. An alternative explanation emerges from the fact that PPAR-γ has been shown to modulate a distinct but partially overlapping set of inflammatory genes relative to corticosteroids.²⁰ Further studies examining the relative effects of rosiglitazone on corticosteroid and PPAR-γ-specific functional outputs are indicated in smokers with asthma and other conditions that are associated with relative corticosteroid insensitivity.

The improvement seen in FEF₇₅ at 14 days and FEF_{25–75} at both 14 and 28 days is of interest, given that there are currently few therapies available for the treatment of small-airway obstruction. Small-airway obstruction, seen in many pulmonary conditions,^{21–23} is associated with dynamic hyperinflation, reduced tolerance to exercise, and increased dyspnea. Given the improvement seen in our patients, consideration should be given to studying PPAR-γ agonists in subjects with small-airway obstruction.

In conclusion, this trial—to our knowledge, the first to examine the efficacy of a PPAR-γ agonist in subjects with asthma—has demonstrated modest improvements in lung function measurements in a group of smokers with mild to moderate asthma. Our conclusions are tempered by the exploratory nature of this work, reflected in the short duration of treatment and the small number of subjects involved. Given that we have detected an effect in a treatment-resistant group, further trials should be undertaken to examine PPAR-γ agonists in asthma and other obstructive airway conditions. Issues that should be addressed in future trials include dose response,

interaction with corticosteroids,^{19,24} PPAR- γ polymorphisms,²⁵ and PPAR- γ endobronchial expression response to treatment.²⁶ PPAR- γ agonists may represent a new therapeutic class for inflammatory diseases.

METHODS

Subjects. Patients with mild to moderate¹ stable asthma, aged 18–60 years, and on $\leq 1,000$ μg of beclometasone dipropionate (or equivalent) per day and smokers of 5 or more cigarettes per day with at least 5 pack-years of smoking history were eligible for enrollment. All subjects demonstrated reversible airflow obstruction.²⁷ Exclusion criteria included diabetes, recent myocardial infarction, and other active pulmonary diseases (full criteria available at <http://www.clinicaltrials.gov>; NCT00119496). Patients were recruited from general practice, hospital clinics, and research databases. The West Glasgow Research Ethics Committee approved the study, and all patients gave written informed consent.

Study design. The study was a randomized, prospective, double-blind, double-dummy, active comparator, parallel-group design. Subjects were monitored for asthma stability for up to 6 weeks and underwent a corticosteroid weaning and monitoring phase that lasted 1 month within this period. All the subjects were treated with inhaled β_2 -agonist alone for 2 weeks and were excluded from randomization if they experienced an exacerbation of asthma at any point during this run-in phase.

If subjects were stable and met entry criteria at the end of the 2-week corticosteroid-free period (including bronchodilator reversibility), they attended a randomization visit that entailed spirometry and peak expiratory flow recordings, completion of an ACQ,²⁸ induced sputum expectoration for differential cell count and supernatant mediators, and routine blood tests for safety (full blood count and renal and liver function tests) and characterization (levels of total and specific immunoglobulin E; total, low-density lipoprotein, and high-density lipoprotein cholesterol; and triglycerides).

The subjects were then randomized with equal bias to one of four groups. Two of the treatment arms and their corresponding results are not discussed in this article.¹³ The subjects discussed in this article received either 4 mg twice a day of oral rosiglitazone maleate (Avandia; GlaxoSmithKline, Greenford, UK) or 100 μg twice a day of inhaled hydrofluoroalkane beclometasone dipropionate (Qvar; IVAX, Runcorn, UK) (equivalent to ~ 400 μg per day chlorofluorocarbon beclometasone dipropionate).²⁹ The subjects returned for prebronchodilator lung function tests at 2 weeks and repeated the assessments carried out at baseline after 4 weeks.

Measurements. Lung function assessments conformed to consensus guidelines.²⁷ Sputum induction, differential count, and supernatant analysis were performed as previously described.^{11,30} Sputum supernatants were collected for determination of interleukin-8 and myeloperoxidase (interleukin-8; R&D Systems, Abingdon, UK; myeloperoxidase; Immundiagnostik, Oxford Biosystems, Oxford, UK). Local hospital laboratories performed the full blood counts, urea and electrolyte determinations, liver function tests, total and specific serum immunoglobulin E tests, and total and differential cholesterol tests.

Continuation of smoking during the study was confirmed by history and the detection of urinary nicotine metabolites, using the SmokeScreen system (GFC Diagnostics, Bicester, UK). Subjects were regarded as current smokers if their category was “mild smoker” or greater and their urine cotinine level was >1.1 mg/ml. Treatment compliance was assessed by tablet count and inhaler weight.

Statistical analysis. Because of the reduced response to inhaled corticosteroids in smokers with asthma and the lack of published information on the effect of thiazolidinediones in asthma, we were unable to perform standard power calculations. The study was informed using FEV₁ changes

from a previous clinical trial with oral corticosteroids in smokers with asthma.⁵ This led us to estimate that we needed to recruit 22 subjects per group to detect a 230 ml difference in FEV₁ between the treatment arms, allowing for a 10% dropout rate. There was a slightly higher dropout rate (13%) in the trial, resulting in a short time extension to allow a larger number of subjects to be randomized to treatment.

The primary end point was the difference in prebronchodilator FEV₁ between the group on rosiglitazone and the one on beclometasone dipropionate at 28 days. The secondary end points were changes in pre- and postbronchodilator peak expiratory flow, forced vital capacity, FEF_{25–75}, FEF₇₅, and ACQ. Exploratory end points were changes in sputum differential, sputum supernatant, and serum cytokines. The randomization schedule was generated in blocks using a validated system (RandAll). Lung function changes were examined with analysis of covariance (incorporating the Kenward–Rogers method) using SAS v8.2 (SAS Institute, Cary, NC). All data obtained after day 1 of treatment were used for analysis. The remaining statistical analysis was performed using Minitab 15 (Minitab, State College, PA). The level of statistical significance was set at <0.05 . Parametric data were examined using paired *t*-testing, two-sided *t*-testing, or analysis of variance, and nonparametric data were analyzed with Mann–Whitney or Kruskal–Wallis testing, as appropriate. Given the exploratory nature of the trial, the secondary and exploratory analyses were not corrected for type 1 errors due to multiple comparisons.

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CONFLICT OF INTEREST

P.B. and L.S. are employees of and own shares in GlaxoSmithKline. The other authors declared no conflict of interest.

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