Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomized controlled trial

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Abstract

Background
Airway inflammation in chronic obstructive pulmonary disease (COPD) is characterized by infiltration of CD8+ T cells and CD68+ macrophages and an increased number of neutrophils, whereas few studies have described the presence of eosinophils. Although anti-inflammatory effects of corticosteroids in stable COPD are unclear, recent studies suggest that combination therapy could be beneficial. We therefore evaluated combined salmeterol/fluticasone propionate (SFC) and fluticasone propionate (FP) alone on inflammatory cells in the airways of COPD patients.

Methods
Patients were treated in a randomized, double-blind, parallel-group, placebo-controlled trial with either a combination of 50µg salmeterol and 500µg FP twice daily ([SFC] n=19, 19 male, mean age 62), 500µg FP twice daily (n=20, 15 male, mean age 64), or placebo (n=21, 17 male, mean age 66) for 3 months. At the start and end of treatment, bronchoscopy with bronchial biopsies

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was performed, and numbers of CD8+ T lymphocytes, CD68+ macrophages, neutrophils and eosinophils were measured.

**Results**
CD8+ cells were significantly reduced by SFC compared with placebo (difference -98.05 cells/mm²; 95% CI -143.14 to -52.9; p<0.001). Such a marked effect was not seen with FP alone (-44.67 cells/mm²; 95% CI -90.92 to 1.57; p=0.06). CD68+ macrophages were also reduced by SFC compared with placebo (difference -31.68 cells/mm²; 95% CI -61.07 to -2.29; p=0.03) but not by FP. SFC did not significantly change neutrophils and eosinophils compared with placebo.

**Conclusions**
SFC has airway anti-inflammatory effects not seen with inhaled corticosteroids alone.

**Abstract word count:** 249

**Key words**
Chronic obstructive pulmonary disease, COPD, airway inflammation, fluticasone propionate, salmeterol, combination therapy, bronchoscopy, biopsy
Introduction
Chronic obstructive pulmonary disease (COPD) is a multi-component disease characterized by progressive airflow limitation that is not fully reversible. Central to its pathogenesis is a chronic inflammatory process throughout the airways, parenchyma and pulmonary vasculature, resulting in many structural changes[1].

The predominant pattern of airway inflammation in COPD is a prevalence of T-lymphocytes and macrophages, which have been shown to correlate with disease severity. T-lymphocytes, with a greater increase in CD8+ than in CD4+ T cells, have been shown to relate to lung destruction and inversely to lung function decline[2,3,4]. CD68+ macrophages appear to play a pivotal role in COPD[5,6,7]. A correlation has been demonstrated between macrophages in the airways and parenchymal destruction, chronic exposure to cigarette smoke, and COPD severity[2,3,7,8,9]. Neutrophils are also increased within COPD airways[10,11], although their role is not completely understood. They have been associated with COPD disease severity and with the rate of decline in lung function[5,12] as they have the capacity to induce tissue damage through the release of various oxidants, and proteases. Increased numbers of eosinophils have also been reported, however their role in COPD remains questionable[13].

Although there is evidence that inhaled corticosteroids reduce COPD exacerbations[14], their beneficial effects on airway inflammation in stable COPD appear limited[15,16]. However, a combination of long-acting β2-agonist and inhaled corticosteroid not only reduces exacerbations in COPD, but improves lung function and symptom control[17,18,19] to a greater extent than either component alone. Recently, combination therapy has been shown to reduce airway inflammation in COPD[20].

To date, however, there has been no comprehensive study examining differences in the effects of combination therapy and inhaled corticosteroids alone on the inflammatory profile in COPD airways. We postulated that a combination of a long-acting β2-agonist with an inhaled corticosteroid, and to a lesser extent inhaled corticosteroid alone, would reduce airway inflammation, specifically CD8+ T cells, and CD68 + macrophages in COPD after 3 months' therapy. Furthermore as a secondary outcome in this study, we set out to investigate the treatment effect on neutrophils and eosinophils, and the relationship of anti-inflammatory effects to clinical outcomes (lung function as assessed by forced expiratory volume in one second [FEV1], and health-related quality of life as assessed by the Chronic Respiratory Questionnaire [CRQ]) in patients with COPD.

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Methods

Patient Population
Sixty subjects with a clinical diagnosis of COPD\textsuperscript{[21]}, were recruited between September 2002 and April 2005 from two respiratory centres, the Montreal Chest Institute and Hôpital Laval, Canada. Subjects were eligible for this study if they met the following criteria: age $\geq 40$ and $\leq 75$ years; smoking history ($\geq 10$ pack years); post-bronchodilator FEV$_1$ $\geq 25\%$ of predicted value and FEV$_1$/FVC $\leq 0.70$. No history of asthma, atopy (as assessed by an allergy skin prick test during screening), or any other active lung disease. Patients on home oxygen, or with elevated pCO$_2$ ($>44$ mmHg), $\alpha_1$-antitrypsin deficiency, recent exacerbation (in the last 4 weeks), uncontrolled medical condition, or hypersensitivity to inhaled corticosteroids and bronchodilators were not eligible. Short-acting bronchodilators, short and long-acting anticholinergics, or theophylline were allowed throughout the study. Oral corticosteroids and/or antibiotics could only be given in short courses for exacerbation treatment. The study was approved by the research ethics committees at the participating centers, and all patients gave written informed consent to participate.

Study Design
This study was designed as a double-blind, randomized, placebo-controlled parallel-group clinical trial, with subjects allocated to receive treatment with salmeterol xinafoate/fluticasone propionate (SFC; Advair\textsuperscript{TM}/Seretide\textsuperscript{TM}/Viani\textsuperscript{TM}, GlaxoSmithKline) Diskus\textsuperscript{TM} (50/500 $\mu$g BID), fluticasone propionate (FP; Flovent\textsuperscript{TM}/Flixotide\textsuperscript{TM}, GlaxoSmithKline) Diskus (500 $\mu$g BID) or matched placebo Diskus (BID). Randomization was performed using a central computer-generated list of random numbers which was stratified by center and which used a block size of six set up by a data management/randomization company, GEREQ, in Montreal, Quebec. A procedure was established by GEREQ, who were in possession of the treatment code, to ensure that the treatment code would be broken only in accordance with the protocol and the criteria set up for unblinding the study (e.g. due to a serious adverse event possibly related to the study treatment).

The total study duration was 16 weeks. After a 4-week washout period from inhaled corticosteroids and long-acting $\beta_2$-agonists, subjects were randomized to one of the treatment groups for 12 weeks. Bronchial biopsies were obtained at Visit 2, prior to treatment initiation, and after 12 weeks of treatment at Visit 4 at the end of study. Spirometry measurements pre- and post-bronchodilator (FEV$_1$ and FVC) and administration of the Chronic Respiratory Questionnaire (CRQ)\textsuperscript{[22]} were performed at Visit 2 and after 4 and 12 weeks of treatment. The ATS-DLD 78 questionnaire\textsuperscript{[23]} was administered at Visit 2 and measurements of lung volumes and transfer factor (D$_L$CO) were made. Bronchoalveolar lavage (BAL) fluid was collected following the bronchoscopy procedure and sputum induction was performed on 3 occasions (2-4 days prior to bronchoscopy at randomization, after 4 weeks of treatment and at the end of treatment); analysis of these samples has not yet been completed and will be the subject of a future publication.
Tissue Preparation
With the use of an Olympus BF fiberoptic bronchoscope, endobronchial biopsy specimens were obtained according to American Thoracic Society guidelines[24]. Six specimens from the subsegmental bronchus were obtained from the right lower, middle and upper lung using cup forceps. In preparation for immunocytochemistry, the bronchial biopsies were fixed accordingly, and processed as either frozen sections, or paraffin embedded sections as previously described[25,26]

Immunocytochemistry
In order to phenotype the inflammatory cells present in the biopsy samples, monoclonal antibodies directed against markers for T lymphocytes (CD8; Vector 4B11), macrophages (CD68; DAKO Diagnostics KP11), eosinophils (MBP; DAKO BMK13) and neutrophils (elastase; DAKO NP57) were used. CD8+ and CD68+ cells were stained on paraffin sections whereas frozen sections were used to detect eosinophils and neutrophils, since these two cell types are not easily detected on paraffin embedded sections.[27] Immunocytochemistry was performed by using a modified Alkaline Phosphatase Antialkaline Phosphatase method as previously described[28]. Briefly, frozen sections were thawed, blocked in Universal Blocking Solution (DAKO Diagnostics) for 15 mins, and incubated with optimum concentration of the primary antibody overnight at 4º C in a humidified chamber. The next day, slides were washed in Tris-buffered saline solution (pH 7.2), incubated with secondary antibody, and finally incubated with mouse alkaline phosphotase antialkaline phosphotase (DAKO). Reactions were then visualized by adding alkaline-phosphotase substrate to the Fast Red (Sigma Chemical Company). Paraffin embedded tissue sections were stained using the Strepavidin Biotin Peroxidase procedure.[29] Briefly, tissue sections were deparaffinized, dehydraded, and blocked in 3% hydrogen peroxide for 5 mins. Antigen retrieval was enhanced by placing sections in a heat-induced epitope retrieval solution (EDTA buffer pH 8.0 for CD8 detection; Tris buffer pH 10 for CD68). Primary antibody was then applied for 1 hour at room temperature. A goat anti-rabbit secondary antibody conjugated to horseradish peroxidase (DAKO K377) was then applied. A colored reaction was achieved by treating the slides with 3-3 diaminobenzidine (Sigma D5637). For negative controls, the primary antibody was replaced by an isotype-matched control antibody.

Not all samples were stained at once, instead they were done in batches, however, we made sure that pre and post biopsies from each individual subject were stained in the same run. Similarly, cell counting was delayed until there were sufficient pre and post biopsies in order to be randomised. The number of positive cells was averaged from six to eight random, non-overlapping fields, from two biopsy samples per subject, and expressed as the mean number of positive cells per square millimetre (mm²). Cell counts were performed blindly by two independent observers using an Olympus light microscope (Carson Group, Markam, Ontario, Canada) with <400X magnification with an eyepiece graticule of 0.202mm². Observers were blinded not only to drug treatment, but also to whether the biopsies were pre or post treatment. The level of agreement between blinded counters was > 90%. The results of cell counts from the two counters were averaged.
Statistical Methods
All data management and data analyses were performed by the authors. The main outcome
variables in this study were the treatment difference in the numbers of CD8+ T-lymphocytes and
CD68+ macrophages in bronchial biopsies. Each endpoint has been analyzed as a change from
baseline. The primary treatment comparisons were between SFC and placebo, and FP and
placebo, and secondary treatment comparisons were between SFC and FP. The secondary
outcome variables were the number of neutrophils and eosinophils in bronchial biopsies. Since at
the time of starting this trial there was no prior study using a combination of inhaled
corticosteroid and long-acting β2-agonist that assessed the airway inflammatory response in
COPD, the sample size was difficult to quantify. Based on a previous study[^16^], and similar
studies in asthma, we estimated the number of patients to be 20 per treatment group for the
primary comparisons. Confidence intervals were provided to estimate the size of any treatment
effects and these were used to determine the clinical relevance of the results. Statistical analysis
was performed using data processed by R, a language and environment for statistical computing
(R Foundation for Statistical Computing; Vienna, Austria). All available on-treatment data were
included in summary and analyses. As expected, some of the data were not normally distributed,
however the difference in the results post minus pre treatment passed the test for normality in all
cases. As such, data were analyzed by Anova tests with Tukey Honest Significant Comparisons *a
posteriori*. Since the main outcome was limited to CD8+ T-lymphocytes and CD68+
macrophages in bronchial biopsies, and the different endpoints in this study were considered to
represent separate pathways, they were treated independently and no adjustments for multiplicity
were performed.
Results

Sixty eligible subjects were randomized to treatment; 19 were randomly assigned to the SFC treatment arm, 20 to the FP arm, and 21 to the placebo arm (see Figure 1). Five subjects refused to have bronchoscopy performed and four subjects did not provide a post-treatment biopsy because they withdrew prematurely. Thus, biopsy data before and after treatment were available for analysis from 51 subjects (19 treated with SFC, 17 treated with FP and 15 treated with placebo). One patient in the placebo group received treatment for only 2 months. The demographic characteristics, smoking history, baseline lung function, respiratory symptoms and prior respiratory medications of randomized patients are summarized in Table 1. Patients were primarily male, half of the patients were currently smoking, and most of them (83%) had a disease severity of II to IV according to GOLD (Global initiative for Obstructive Lung Disease) Stages[21].

Primary endpoint

Following 12 weeks of treatment, a statistically significant fall from baseline in the numbers of CD8+ T-lymphocytes (p<0.001) and CD68+ macrophages (p=0.008) was demonstrated after treatment with SFC, but not with FP alone (Table 2). As shown in Figure 2, the mean differences in the number of CD8+ T-lymphocytes and CD68+ macrophages between SFC and placebo were statistically significant (p<0.001 and p= 0.03 respectively). The mean differences in CD8+ T-lymphocytes and CD68+ macrophages between FP and placebo failed to reach statistical significance. The mean differences of CD8+ T-lymphocytes and CD68+ macrophages between SFC and FP were statistically significant (p=0.01 and p=0.04 for CD8+ cells and CD68+ cells, respectively).

Secondary endpoints

Neither treatment had significant effects on the low numbers of biopsy neutrophils and eosinophils, although there was an increase from baseline in neutrophil numbers with FP that approached statistical significance (p=0.07, Table 2). Although there was no significant difference in the number of neutrophils between SFC and placebo, the number of neutrophils was significantly lower for SFC than for FP alone (p<0.001) (Figure 2). Furthermore, the comparison between FP and placebo showed a lower number of neutrophils in the placebo arm (p=0.005). No statistically significant differences were seen between treatments for the number of eosinophils.

Clinical outcomes

No evidence of improvement in clinical outcomes was observed, as measured by lung function as well as health related quality of life questionnaires. The post bronchodilator % predicted FEV1 was similar at baseline and post-treatment in the SFC and FP treatment group and a decrease of 6% from baseline was seen in the placebo group. Clinically, all treatments were well-tolerated, and only one patient (treated with FP) experienced a drug-related adverse event (candidiasis). Three patients experienced post-bronchoscopy pneumonitis that was thought to be associated with the BAL procedure.

Discussion

Our study has shown that the combination of salmeterol and FP reduces aspects of airway inflammation in patients with COPD and that these effects are not observed with FP alone. We have demonstrated a reduction in CD8+ T-lymphocytes and CD68+ macrophages following 12
weeks of treatment with combination therapy. Both these cell types appear to be important in the pathogenesis of COPD\cite{4,5,6}. Treatment with FP did not have these effects, giving only small, non-significant decreases in the number of CD8+ cells compared with placebo and having no effects on CD68+ macrophages. Combination treatment reduced neutrophil number counts compared to FP treatment but not compared to placebo. We did not demonstrate an effect of either active treatment on eosinophils in bronchial biopsies. The numbers of eosinophils observed in the airways of these stable COPD patients was low and our data do not provide support for an important role for these cells in stable COPD.

COPD is recognized as an inflammatory disease\cite{21} and so treatments that reduce inflammatory cells in patients with COPD may be of importance in therapeutic management. CD8+ cells in the airways and lung parenchyma have been shown to correlate significantly with the degree of airflow limitation suggesting that CD8+ cells may be related to the progression of the disease\cite{4}. Cytotoxic CD8+ cells have the potential to release mediators such as TNF-\(\alpha\), IFN-\(\gamma\), perforins, and granzymes, leading to the lung destruction. Increased macrophage numbers in the airways are associated with parenchymal destruction and COPD severity\cite{2,7,9}. CD68 macrophages mainly release TNF-\(\alpha\), proinflammatory cytokine which is involved in systemic inflammation, as well as tissue hypoxia and muscle wasting seen in COPD.\cite{30}

Reduction of CD8+ cells by SFC in the airways of patients with COPD has also been demonstrated in a recent study by Barnes and colleagues\cite{20}. That study, however, did not include an inhaled corticosteroid treatment group and so our results in addition to confirming the effects of combination treatment on CD8+ cells also provide evidence that in large part the effect is not related to the action of inhaled corticosteroids alone. In contrast to these investigators, we also observed an effect of combination treatment on CD68+ macrophages, providing further evidence for enhanced anti-inflammatory effects of combination treatment. Effects on macrophages have not been observed with inhaled corticosteroids alone\cite{16}. Our results demonstrating an increased number of neutrophils following FP treatment, were not surprising, yet they further support the possibility that corticosteroids inhibit neutrophilic apoptosis, thus prolonging their survival, as previously shown.\cite{31} The failure to show a significant change in neutrophil counts following combination treatment however, may have resulted from the ability of salmeterol to reduce the number of neutrophils by promoting their apoptosis and reducing levels of IL-8, a key neutrophil chemoattractant. Although these effects have been well established in vitro and in asthma\cite{32}, only a salmeterol treatment arm in this study design could confirm this possibility in COPD.

One limitation of the study is that we cannot extrapolate that the inflammatory changes are responsible for the improvement in clinical outcomes shown in previous studies. For example in the Barnes study, the anti-inflammatory effect of SFC was accompanied by significant improvements in lung function.\cite{20} Our study was not powered to detect an effect on clinical outcomes and furthermore, the study was of relatively short duration which may have limited the possibility to show any benefit on quality of life. This study was also not designed to assess effects on COPD exacerbation; previous studies have shown that a reduction in exacerbations has been observed with combination therapy\cite{17}. The biopsies in this study were taken from the proximal rather than the distal airways, which is a clear limitation in this study. The reason being, that proximal airways may not closely reflect all the pathologic changes present in peripheral airways and lung parenchyma, which are the sites generally responsible for airflow limitation in

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COPD\textsuperscript{[33]}. However, increases in CD8+ cells have been observed in both the proximal and distal airways where a relationship between their numbers and reduced lung function has been shown\textsuperscript{[3,34,35]}. As such, the site of the biopsy is possibly the reason for the discrepancy in inflammatory and clinical responses.

Subjects were allowed to use short acting beta\textsubscript{2} agonists both during the run-in period and during the study. Although one of the measures of interest was the interaction between inhaled corticosteroids and beta\textsubscript{2} agonists, this is unlikely to have biased the results. Randomisation will tend to make study groups comparable and patients were kept blind to the assigned therapy. There is increasing evidence to suggest a synergistic and/or additive effect of long-acting $\beta_2$-agonists and inhaled corticosteroids on airway inflammation\textsuperscript{[36,37,38,39]}. Although, the mechanisms for this observation are not entirely clear, \textit{in vitro} studies suggest that corticosteroids may regulate $\beta_2$-receptor function by increasing expression of the receptor and by restoring G-protein/$\beta_2$-receptor coupling and inhibiting $\beta_2$-receptor downregulation. By modulating glucocorticoid receptor phosphorylation, long-acting $\beta_2$-agonists prime the glucocorticoid receptor and affect its nuclear localization. This interactive mechanism presumably leads to additive and/or synergistic effects of combination therapy on airway inflammation\textsuperscript{[35,38]}. Long-acting $\beta_2$-agonists may also have non-bronchodilator effects which are anti-inflammatory\textsuperscript{[40]}. They have been shown to inhibit mediator release from macrophages\textsuperscript{[41]}, and in patients with asthma reduce the number of neutrophils in bronchial biopsies\textsuperscript{[32]}. The design of our study does not allow us to define the effects of treatment with salmeterol alone in patients with COPD.

In summary, this study provides evidence of anti-inflammatory effects in patients with COPD for the combination of an inhaled corticosteroid and long-acting $\beta_2$-agonist that are not observed with inhaled corticosteroid alone. The enhanced effects of combination therapy on key inflammatory cells may explain the clinical efficacy that has been shown in previous COPD trials. Combination therapy reduced CD8+ cytotoxic T-lymphocytes and CD68+ macrophages, cells that have been shown to be correlated with COPD disease severity and recognized to be important in the pathogenesis of COPD. However, a long term study will be needed to determine if combination therapy can modify the progressive nature of this disorder.
Acknowledgements
We are indebted to the following persons, without whose support this study could not have been successfully completed: Marthe Bélanger, RN, from Hôpital Laval, Institut Universitaire de Cardiologie et de Pneumologie de l’Université Laval; Leo Cicora, RT and Elizabeth Sukhdeo, RT from the Montreal Chest Institute, McGill University Health Centre.

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References


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Figure Legends

Figure 1: Flowchart of patient disposition through the study

Figure 2: Treatment Differences for CD8 T Lymphocytes, CD68 Macrophages, Eosinophils and Neutrophils. *Data expressed as the mean difference in the number of cells and the 95% confidence interval.*
### Table 1: Patients' Baseline Characteristics

<table>
<thead>
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<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Number randomized</td>
<td>19</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Male/Female (n)</td>
<td>19/0</td>
<td>15/5</td>
<td>17/4</td>
</tr>
<tr>
<td>Current smokers/Former smokers (n)</td>
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<td>10/10</td>
<td>8/13</td>
</tr>
<tr>
<td>GOLD Stages (n)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I: FEV1 ≥ 80%</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>II: 50% ≤ FEV1 &lt;80%</td>
<td>6</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>III-IV: FEV1 ≤ 50%</td>
<td>9</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory medications before study (n)</td>
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<td></td>
<td></td>
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<tr>
<td>Short-acting bronchodilators</td>
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<td>13</td>
<td>13</td>
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<tr>
<td>Long-acting anticholinergic agent</td>
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<td>3</td>
</tr>
<tr>
<td>Long-acting β2-agonists</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Long-acting β2-agonists/inhaled corticosteroids</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Theophylline</td>
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<td>0</td>
<td>0</td>
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</table>

* FEV1 Reversibility calculated as: *(post-BD FEV1 (L) – pre-BD FEV1 (L)) / pre-BD FEV1 (L) x 100%*
Table 2: Biopsy Cell Counts (cells/mm²) according to Treatment Allocation

<table>
<thead>
<tr>
<th></th>
<th>SFC (N=19)</th>
<th>FP (N=17)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8+ T-Lymphocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-treatment mean</td>
<td>107[31]</td>
<td>164[67]</td>
<td>201[48]</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-84[67]</td>
<td>-31[47]</td>
<td>14[41]</td>
</tr>
<tr>
<td>Median change from baseline</td>
<td>-75 (-110 to -34)</td>
<td>-24 (-51 to -15)</td>
<td>11 (-4 to 41.50)</td>
</tr>
<tr>
<td>P-value for mean change from baseline</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td>0.42</td>
</tr>
<tr>
<td>CD68+ Macrophages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>102[37]</td>
<td>122[49]</td>
<td>135[53]</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-29[22]</td>
<td>0[33]</td>
<td>2[49]</td>
</tr>
<tr>
<td>Median change from baseline</td>
<td>-30 (-41 to -10)</td>
<td>-2 (-15 to 30)</td>
<td>20 (-38 to 34)</td>
</tr>
<tr>
<td>P-value for mean change from baseline</td>
<td>0.008</td>
<td>0.98</td>
<td>0.88</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median change from baseline</td>
<td>-11 (-19 to 0.5)</td>
<td>18 (6 to 21)</td>
<td>-4 (-11 to 7.5)</td>
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<tr>
<td>P-value for mean change from baseline</td>
<td>0.16</td>
<td>0.07</td>
<td>0.62</td>
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<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median change from baseline</td>
<td>0 (-3 to 3)</td>
<td>-1 (-2 to 3)</td>
<td>1 (0.5 to 7)</td>
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<tr>
<td>P-value for mean change from baseline</td>
<td>0.80</td>
<td>0.61</td>
<td>0.09</td>
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</table>

Data expressed as mean (standard deviation), and as median (interquartile ranges).

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Running head: Treatment effects on airway inflammation
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Figure 1.

Assessed for eligibility (n=62)

Enrollment

Randomization

Excluded (n=2)

Not meeting inclusion criteria: (n=2)

Salmeterol/Fluticasone (n=19)
Received allocated intervention (n=19)
Discontinued intervention (n=0)
Refused Bronchoscopy (n=0)

Fluticasone Propionate (n=20)
Received allocated intervention (n=20)
Discontinued intervention (n=1)
Reason: Patient developed candidiasis
Refused Bronchoscopy (n=2)

Placebo (n=21)
Received allocated intervention (n=21)
Discontinued intervention (n=3)
Reasons: Patient’s decision/withdrew consent (n=2); malignant cervical nodule diagnosed (n=1)
Refused Bronchoscopy (n=3)

Analyzed (n=19)
Excluded from analysis (n=0)

Analyzed (n=17)
Excluded from analysis (n=0)

Analyzed (n=15)
Excluded from analysis (n=0)
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