High altitude treatment in atopic and non-atopic patients with severe asthma

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Abstract

**Background:** The beneficial effects of high altitude treatment in asthma have been attributed to allergen avoidance. Recent evidence shows that this treatment improves airway inflammation in non-allergic patients as well. We hypothesized that high altitude treatment is clinically equally effective in patients with severe refractory asthma, with or without allergic sensitization.

**Methods:** In a prospective observational cohort study, 137 adults with severe refractory asthma (92 with allergic sensitization), referred for high altitude treatment in Davos (1600 m) were consecutively included. We measured asthma control (ACQ), asthma-related quality of life (AQLQ), sino-nasal symptoms (SNOT-20), medication requirement, post bronchodilator (pb)FEV₁, 6 min. walking distance (6MWD), total IgE, blood eosinophils, and exhaled nitric oxide (FeNO) at admittance and after 12 weeks.

**Results:** Sensitized and non-sensitized patients showed similar improvements in ACQ (-1.4 and -1.5; p=0.79), AQLQ (1.6 and 1.5; p=0.94), SNOT-20 (-0.7 and -0.5; p=0.18), pbFEV₁ (6.1% and 5.8% pred.; p=0.87), 6MWD (+125 m and +147 m; p=0.43) and oral steroids (40% vs 44%; p=0.51). Sensitized patients showed a larger decrease in total IgE, blood eosinophils and FeNO.

**Conclusions:** High altitude treatment improves clinical and functional parameters, and decreases oral corticosteroid requirement in patients with severe refractory asthma, irrespective of allergic sensitization.
Keywords

Air pollution, corticosteroids, house dust mite
Introduction

The majority of patients with mild to moderate asthma can be treated adequately with inhaled corticosteroids combined with long-acting bronchodilators [1]. However, this therapy is not sufficient to reach asthma control in patients with severe refractory asthma [2]. For these patients there are only few effective therapeutic options available, including systemic corticosteroids, which have serious adverse effects [3], and monoclonal antibodies against immune globulin E, which are indicated only for patients with allergic asthma [4]. For non-atopic patients with severe asthma, however, there is an urgent need for better therapies [5].

High altitude treatment has been applied for decades in patients with asthma, especially in children and adolescents with moderate to severe atopic disease [6-9]. The success of this treatment has long been attributed to the absence of house dust mite allergens at altitudes above 1600 m [10]. However, two recent studies, one in children, and one in adults have shown that high altitude treatment also reduces airway inflammation in patients with other allergies than house dust mite, or no allergies at all [11, 12]. This suggests that other factors than allergen avoidance contribute to the beneficial influence of high altitude treatment, and that this treatment might be a valuable therapeutic option for patients with severe, non-atopic asthma.

The present prospective observational study was designed to test the hypothesis that high altitude treatment is equally effective in severe asthmatic patients with or without house dust mite allergy and with or without any allergies. To that end we compared the effects of 12 weeks high altitude treatment on clinical, physiological and inflammatory parameters, between patients with severe refractory asthma with and without sensitization to house dust mite or other aeroallergens, who were referred to the Dutch Asthma Centre in Davos for high altitude treatment.
**Patients and methods**

**Patients**

Between January 2008 and January 2010 all adult patients who were referred to the Dutch Asthma Centre Davos in Switzerland with a diagnosis of severe, refractory asthma according to ATS criteria [13] were asked to participate in the study. They all used high doses of inhaled corticosteroids (≥1260 µg·day of beclomethasone or equivalent) or oral corticosteroids combined with long-acting bronchodilators for at least 1 yr. All patients were symptomatic and had at least one severe exacerbation during the past year requiring a course of oral corticosteroids, or were receiving chronic oral corticosteroid therapy. All patients were non-smoking or ex-smoker. In order to exclude patients with smoking related COPD, patients with a smoking history > 15 years, had to show reversibility in FEV₁ to short-acting beta agonist >12 % predicted. **Before being referred to the high altitude clinic inhalation technique, adherence with treatment, and optimal avoidance of exposure to allergens and cigarette smoke was checked by a questionnaire completed by the referring pulmonologist.** The study was approved by the Ethics Committee of the Academic Medical Centre of the University of Amsterdam (Amsterdam, the Netherlands). All patients gave their written informed consent. This study was registered at the Netherlands Trial Register, under NTR 1277.

**Study design**

We conducted a 12 weeks prospective observational cohort study in patients with severe, refractory asthma who were referred to the Dutch Asthma Centre in Davos for
high altitude treatment in order to optimize their disease. Patients were assessed and evaluated according to a systematic protocol at entry and after a 12 week multidisciplinary comprehensive treatment.

**High altitude treatment: climate and specialized treatment**

The high altitude climate offers an environment with low levels of allergic and non-allergic bronchoconstricting stimuli. The multidisciplinary treatment at high altitude consists of a personalized, structured, comprehensive treatment plan aimed at achieving full asthma control and improving patient’s physical condition with the lowest possible dose of asthma medication. The quintessence of the treatment is the daily supervised exercise training indoors and outdoors in the trigger free environment.

**Questionnaires**

All patients filled in standard questionnaires including questions about current symptoms, medical history, age at asthma onset, smoking habits and medication usage. The dose of inhaled corticosteroids was expressed in equivalents of inhaled beclomethasone and the dose of oral corticosteroids in mg prednisolone equivalents.

The 6-item Juniper Asthma Control Questionnaire (ACQ) was used to assess the level of asthma control [14]. Responses to each item are rated on a 6-point scale. The mean of the 6 items in the ACQ between 0 (totally controlled) and 6 (severely uncontrolled) was used.
The Juniper Asthma Quality of Life Questionnaire, standardized version (AQLQ(S)) [15] was used to measure asthma related quality of life. The mean of the 32 items in the AQLQ between 1 (very poor quality of life) and 7 (best quality of life) was used.

The rhino-sinusitis health status was measured by the 20-question Sino-Nasal Outcome test (SNOT-20), the possible range of the SNOT-20 score is 0 to 5, with a higher score indicating a greater rhino-sinusitis-related health burden [16].

**Pulmonary function**

Spirometry: Forced expiratory volume in one second ($FEV_1$) was assessed before and after inhaled administration of 400 µg salbutamol and expressed as percentage of predicted value (%pred.). Predicted values were obtained from Quanjer and co-workers [17]. **Six-minute walk tests were performed according to ATS guidelines** [18].

**Allergy tests**

Total IgE in peripheral blood was assessed by fluroenzyme immunoassay UniCAP® (Pharmacia & Upjohn, Uppsala, Sweden) and expressed in kU/L. Sensitization to Specific IgE was assessed with a panel of common aero-allergens (house dust mite, mixed grass and birch pollen, cat and dog dander, aspergillus) UniCAP® (Pharmacia & Upjohn, Uppsala, Sweden) and expressed in kU/L. Patients were classified as sensitized to house dust mite if IgE to house dust mite was >0.35 kU/L.

**Markers of systemic and airway inflammation**
Eosinophils in peripheral blood were measured by standard automated cell counter. Fractional exhaled Nitric oxide (FeNO) was measured by a chemiluminescence analyser (Niox Aerocrine AB, Solna, Sweden) [19].

**Statistical analysis**

Changes in clinical, functional and immunological parameters from admission to discharge were analysed by T-tests and Wilcoxon signed rank test for paired samples. Unpaired T-tests and Mann-Whitney were used to analyse the differences between groups. A p-value of <0.05 was considered statistically significant. SPSS 17.0 (SPSS Inc., USA) was used for the analysis.
Results

Of 180 patients who were asked to participate in the study, 4 patients refused for personal reasons. 137 patients completed the 12 week follow-up period and were included in the analysis. The other 39 patients left Davos at an earlier time-point. There were no differences in baseline characteristics between patients who did and did not participate in the study (data not shown). Patient characteristics at baseline are shown in table 1a for 68 house dust mite sensitized and the 69 non-house dust mite sensitized patients. In table 1b the characteristics of 92 patients with any sensitization to common aeroallergens and 45 without sensitization are shown. Changes from baseline in clinical, physiological and inflammatory parameters in patients with and without sensitization to house dust mite are shown in Table 2, and with and without sensitization to any aeroallergen in Table 3.

After 12 weeks high altitude treatment improvements in asthma control, asthma-related quality of life, sino-nasal symptoms, \( \text{FEV}_1 \), \( \text{6-MWD} \) and total IgE were observed in patients with and without sensitization to house dust mite, while the daily requirement for oral corticosteroids was decreased. Fourteen out of 29 (48 %) patients sensitized to house dust mite and 15 out of 41 (36 %) patients without house dust mite sensitization could discontinue maintenance treatment with oral steroids completely. In the patients who could not discontinue oral corticosteroid treatment, the mean daily dose of prednisolone equivalent decreased from mean (SD) \( \text{26.3 (13.3)} \) to 14.3 (10.3) mg (\( p = 0.006 \)) in those sensitized to house dust mite, and from \( \text{29.2 (24.0)} \) to 14.4 (8.8) mg (\( p = 0.001 \)) in the non-house dust mite sensitized patients.
There was a decrease in peripheral blood eosinophils and exhaled nitric oxide in patients with house-dust mite sensitization, which was not observed in non-house dust mite sensitized patients. The effects of high altitude did not differ between patients with or without sensitization to house dust mite for all other parameters (Table 2).

Similar results were obtained when comparing the effects of high altitude treatment between patients with or without sensitization to any airborne allergens (Table 3, figure 1 and 2). Both allergic (N= 92) and non-allergic (N= 45) patients with severe asthma showed improvements in clinical and physiological parameters. However, improvements in total IgE levels, peripheral blood eosinophils and exhaled nitric oxide were observed only in patients with severe allergic asthma.
Discussion

This study shows that patients with severe refractory asthma benefit from high altitude treatment irrespective of sensitization to house dust mite, or any common aero-allergen. The beneficial effect in clinical and functional parameters coincides with a decrease in oral corticosteroid requirement. Asthma symptoms, asthma related quality of life, rhino-sinusitis symptoms, lung function and exercise performance improve to a similar extent in sensitized and non-sensitized patients, whereas total IgE, peripheral blood eosinophils and exhaled nitric oxide decrease only in sensitized patients. These findings suggest that high altitude treatment is a valuable treatment option not only for patients with house dust mite allergic asthma, but also for patients with severe, refractory, non-allergic or “intrinsic” asthma.

This is the first study showing improvements in clinical and physiological parameters of high altitude treatment in adults with severe, refractory asthma who are not sensitized to house dust mite. A large number of studies have shown beneficial effects of high altitude treatment on asthma control, asthma related quality of life, airways hyperresponsiveness and markers of inflammation in children and adolescents with house dust mite allergic, moderate to severe asthma [6-9, 20, 21]. Two studies have investigated the effects of high altitude treatment on markers of airway inflammation and observed similar improvement in FeNO in allergic and non-allergic patients, but in these studies the effects on upper and lower airway symptoms, lung function, exercise capacity or medication requirement were not systematically addressed [11, 12].

Our study is unique in that it systematically evaluated the effects of high altitude treatment in a large cohort of well described patients with severe refractory asthma,
and showed that beneficial effects occur irrespective of sensitization to airborne allergens.

In our study, the treatment program was adjusted to the individual needs and capabilities of the patients. Theoretically, this might have introduced a treatment bias. However, the essence of the treatment, being the change in environmental exposure from the polluted, industrialized environment at sea level to the low trigger environment at high altitude was similar for both allergic and non-allergic patients. Moreover, there were no specific treatment adjustments related to the presence or absence of allergic sensitization. Therefore, we do not believe that differences in treatments can explain the results of the present study.

It can also be argued that any individual, even without asthma, might benefit from a stay in the mountain climate. This might be true, but our patients had objective improvements in asthma symptoms, lung function and inflammatory parameters, as well as large improvements in exercise capacity and decreases in oral corticosteroid requirement, suggesting that high altitude climate is particularly beneficial for patients with severe respiratory diseases. The improvements were the more striking since the patients in our study were referred to the high altitude clinic because of long standing very severe, poorly controlled, refractory asthma by pulmonologists who are specialized in asthma care and working in academic hospitals or tertiary referral centres in the Netherlands. Clearly, decrease of exposure to allergens was not the only reason for the beneficial effect, given the similar improvement in sensitized and non-sensitized patients.

How can we explain the beneficial effects of high altitude treatment in non-sensitized patients with severe asthma? Several factors might play a role [22]. First, the
mountain outdoor climate in the Alps not only has very low levels of house dust mite, fungal spores and pollens (Source: Meteoschweiz) but is also far less polluted than the climate in other parts of Europe at sea level such as the Netherlands [23-25]. Second, the high-altitude climate may have a direct physiological benefit because of the lower viscosity of the air and lower oxygen pressure. The decreased density of the air reduces respiratory resistances and increases inspiratory and expiratory flows, promoting full expansion of the lungs and decreasing lung resistance, which makes it easier to breathe. This effect may be comparable to that of other low density gases such as heliox, which has been applied successfully in patients with acute severe asthma [26]. Thirdly, by moving to the mountains, the patients are literally moved away from psychological stress at home or at work [27]. Psychological stress has been shown to enhance airway inflammation by modulating immune cell function through neural and hormonal pathways [28]. Fourthly, the Alps are well known for their abundance of sunshine. Exposure to UV light stimulates vitamin D photosynthesis in the skin and may modulate the immune system, thereby potentially reducing the severity of chronic diseases, such as asthma [29]. Because of all the above qualities, the low-trigger climate at high altitude provides the ideal environment for all patients with severe refractory asthma, sensitized and non-sensitized to house dust mites or common inhalation allergens.

The results of our study have clinical implications. Since the clinical benefits of high altitude treatment are similar in sensitized and non-sensitized patients, there is no reason to restrict this treatment to children and adolescents with atopic asthma and predominant house dust mite allergy [28]. Because of its beneficial effects on asthma control, exercise capacity and corticosteroid requirement, it should be offered to all
patients with severe refractory asthma, including middle-aged and older adults with “intrinsic” disease [31]. The favourable climate at high altitude provides ideal circumstances to participate in pulmonary rehabilitation programs and to improve exercise capacity and physical fitness for prolonged periods of time. Multidisciplinary tailor-made treatment programs such as the one offered by the Dutch Asthma Centre in Davos are likely to lead to better outcomes than similar interventions at sea level, although this has to be confirmed by randomized-controlled trials [32].

In conclusion, we have shown that high altitude treatment is a valuable treatment option for patients with severe refractory asthma, both for patients who are sensitized and not sensitized to airborne allergens. It significantly improves symptoms of the upper and lower airways, asthma related quality of life, lung function, and exercise capacity with a simultaneous reduction in the requirement for oral corticosteroids or even discontinuation of these drugs. High altitude treatment is one of the very few efficacious treatments for patients with severe refractory asthma, and has no adverse effects. It is probably the best therapeutic option for patients with severe non-atopic asthma, for whom there is no other treatment available than systemic corticosteroids to control their disease.

Acknowledgements

We thank the Netherlands-Davos Society for their support.
References


### Table 1a. Baseline characteristics of patients with and without house dust mite sensitization

<table>
<thead>
<tr>
<th></th>
<th>HDM sensitized patients</th>
<th>Non-HDM-sensitized patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=68</td>
<td>N=69</td>
<td></td>
</tr>
<tr>
<td>Female n (%)</td>
<td>50 (73%)</td>
<td>43 (63%)</td>
<td>0.251</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.5 (14.5)</td>
<td>48 (15.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Sensitized for any inhaled allergen n (%)</td>
<td>68(100%)</td>
<td>24 (35%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex smoker n (%)</td>
<td>28 (40%)</td>
<td>22 (32%)</td>
<td>0.321</td>
</tr>
<tr>
<td>BMI</td>
<td>28.8 (5.9)</td>
<td>28.1 (6.9)</td>
<td>0.551</td>
</tr>
<tr>
<td>Age of asthma onset *(years)</td>
<td>4 (0-45)</td>
<td>12 (1-63)</td>
<td>0.001</td>
</tr>
<tr>
<td>Asthma duration* (years)</td>
<td>25 (2-71)</td>
<td>33 (1-65)</td>
<td>0.455</td>
</tr>
</tbody>
</table>

Data are presented as mean(SD) or *median(minimum-maximum) unless otherwise stated. HDM: House Dust Mite. BMI: Body Mass Index

### Table 1b. Baseline Characteristics of patients with and without any allergic sensitization

<table>
<thead>
<tr>
<th></th>
<th>sensitized patients</th>
<th>Non-sensitized patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=92</td>
<td>N=45</td>
<td></td>
</tr>
<tr>
<td>Female n (%)</td>
<td>50 (73%)</td>
<td>35 (78%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 (15.8)</td>
<td>48 (14.2)</td>
<td>0.124</td>
</tr>
<tr>
<td>Sensitized for HDM n (%)</td>
<td>68 (74%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex smoker n (%)</td>
<td>32 (35%)</td>
<td>18 (40%)</td>
<td>0.555</td>
</tr>
<tr>
<td>BMI</td>
<td>28.0 (56.7)</td>
<td>29.4 (5.7)</td>
<td>0.261</td>
</tr>
<tr>
<td>Age of asthma onset *(years)</td>
<td>5 (0-58)</td>
<td>12 (1-63)</td>
<td>0.001</td>
</tr>
<tr>
<td>Asthma duration* (years)</td>
<td>33 (1-71)</td>
<td>24 (3-66)</td>
<td>0.455</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or *median (minimum-maximum) unless otherwise stated. BMI: Body Mass Index
Table 2. Values at baseline and after 12 weeks of high altitude treatment in patients with and without house dust mite sensitization

<table>
<thead>
<tr>
<th></th>
<th>HDM sensitized patients</th>
<th>Non-HDM-sensitized patients</th>
<th>Significance between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=68</td>
<td>N=69</td>
<td></td>
</tr>
<tr>
<td>T=0</td>
<td>T=12wk</td>
<td>p-value</td>
<td>T=0</td>
</tr>
<tr>
<td>ACQ score</td>
<td>3.0 (1.0)</td>
<td>1.6 (&lt;0.001)</td>
<td>3.3 (1.0)</td>
</tr>
<tr>
<td>AQLQ score</td>
<td>4.0 (0.9)</td>
<td>5.6 (&lt;0.001)</td>
<td>3.8 (0.9)</td>
</tr>
<tr>
<td>SNOT-20 score</td>
<td>2.2 (0.8)</td>
<td>1.5 (&lt;0.001)</td>
<td>2.2 (0.76)</td>
</tr>
<tr>
<td>Patients on OCS (%)*</td>
<td>29 (43%)</td>
<td>15 (&lt;0.001)</td>
<td>41 (59%)</td>
</tr>
<tr>
<td>OCS mg/day*</td>
<td>0 (0-60)</td>
<td>0 (&lt;0.001)</td>
<td>5.0 (0-110)</td>
</tr>
<tr>
<td>ICS µg/day*</td>
<td>1600 (200-8000)</td>
<td>1600 (0.533)</td>
<td>1600 (0)</td>
</tr>
<tr>
<td>FEV₁%pred.</td>
<td>88.4 (20.4)</td>
<td>94.2 (20.1)</td>
<td>86.5 (26.2)</td>
</tr>
<tr>
<td>6 MWD*</td>
<td>516 (178)</td>
<td>636 (&lt;0.001)</td>
<td>430 (182)</td>
</tr>
<tr>
<td>Tot IgE kU/L</td>
<td>376 (7-5000)</td>
<td>245 (6-4682)</td>
<td>94 (5-1781)</td>
</tr>
<tr>
<td>Blood Eos*</td>
<td>235 (0-1050)</td>
<td>210 (50-570)</td>
<td>200 (0-880)</td>
</tr>
<tr>
<td>FeNO ppb*</td>
<td>27.6 (5-209)</td>
<td>18.4 (&lt;0.001)</td>
<td>16 (5-224)</td>
</tr>
</tbody>
</table>

Data in mean (SD) or *median (minimum-maximum)

Total immune globulin E(IgE) and blood eosinophils (eos) at 12 weeks were measured in 43 house dust mite (HMD) sensitized and 36 non-HDM sensitized patients.

ACQ: Asthma Control Questionnaire score: (0-6) 0 = well controlled,
AQLQ: Asthma Quality of Life Questionnaire score: (1-7) 7 = best quality of life,
SNOT-20: Sino-Nasal Outcome Test- 20 items score: (0-5) 0 = no complaints
OCS: Oral Corticosteroids
ICS: Inhalation Corticosteroids
6MWD: 6 Minute Walking Distance
FeNO: Fractionated exhaled Nitric Oxide
<table>
<thead>
<tr>
<th></th>
<th>Sensitized patients N=92</th>
<th>Non- sensitized patients N= 45</th>
<th>Significance between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T=0</td>
<td>T=12wk</td>
<td>p-value</td>
</tr>
<tr>
<td>ACQ score</td>
<td>3.1 (1.1)</td>
<td>1.7 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AQLQ score</td>
<td>4.0 (1.0)</td>
<td>5.6 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SNOT score</td>
<td>2.2 (0.8)</td>
<td>1.5 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pt on OCS (%)</td>
<td>45 (49%)</td>
<td>27 (29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OCS mg/day*</td>
<td>0 (0-110)</td>
<td>0 (0-40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICS µg/day*</td>
<td>1600 (200-8000)</td>
<td>1600 (0-8000)</td>
<td>0.295</td>
</tr>
<tr>
<td>FEV1 %pred.</td>
<td>86.9 (22.0)</td>
<td>93 (20.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>6MWD</strong></td>
<td><strong>514 (182)</strong></td>
<td><strong>639 (220)</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Tot IgE kU/L</td>
<td>369 (7-5000)</td>
<td>224 (6-4682)</td>
<td>0.000</td>
</tr>
<tr>
<td>Blood Eos*</td>
<td>250 (0-1050)</td>
<td>220 (50-570)</td>
<td>0.022</td>
</tr>
<tr>
<td>FeNO ppb*</td>
<td>27 (5-224)</td>
<td>18 (1-70)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data in mean (SD) or *median (minimum-maximum)
Total IgE and blood eosinophils at 12 weeks were measured only in 59 sensitized and 20 non- sensitized patients.
ACQ: Asthma Control Questionnaire score: (0-6) 0 = well controlled
AQLQ: Asthma Quality of Life Questionnaire score: (1-7) 7 = best quality of life,
SNOT-20: Sino-Nasal Outcome Test, 20 items score: (0-5) 0 = no complaints
OCS: Oral Corticosteroids
ICS: Inhaled Corticosteroids
6MWD: 6 Minute Walking Distance
LEGENDS TO THE FIGURES

Figure 1
The mean a) Asthma Control Questionnaire (ACQ) score, b) Asthma related Quality of Life Questionnaire (AQLQ) score, c) Sino-Nasal Outcome Test (SNOT) score, d) and 6 Minutes Walking Distance (6MWD) plotted at admittance, and after 6 weeks and 12 weeks high altitude treatment in patients with * and without = sensitization to any allergen.

Figure 2
The mean a) FEV₁, b) level of Fractionated exhaled Nitric Oxide (FeNO) and c) Oral Corticosteroid (OCS) dose at the start of the study and after 6 weeks and 12 weeks high altitude treatment in patients with • and without = sensitization to any allergen. Oral steroid dose was assessed only in patients on maintenance oral corticosteroid treatment at the start of the study.
Figure 1

(a) Mean ACOQ score over time for two groups, showing a significant difference at 12 weeks.

(b) Mean AQLQ score over time for two groups, showing a significant difference at 12 weeks.

(c) Mean SNOT score over time for two groups, showing a significant difference at 12 weeks.

(d) Mean 6MWD (m) over time for two groups, showing a significant difference at 12 weeks.
Figure 2

a) Mean (ab)FEV1 (% predicted)

b) Median FeNO (ppb)

c) Mean Oral steroids (mg)