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Inhaled steroids improve quality of life in patients with steady-state bronchiectasis

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KEYWORDS
Bronchiectasis;
Inhaled steroids;
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Summary
Background: The effects of inhaled steroids upon the quality of life of patients with bronchiectasis remain unknown.
Study objective: To analyze the effect of inhaled fluticasone propionate (FP) for 6 months upon the clinical, functional, microbiological and outcome parameters of patients with steady-state bronchiectasis not due to cystic fibrosis, and its repercussions for patient health-related quality of life (HRQoL).
Design: Prospective, randomized, double-blind (for effective doses) study.
Patients and interventions: The diagnosis of bronchiectasis was made by high-resolution computed tomography. Ninety-three patients (mean age: 68.5 [8.4]) were randomized to receive 250 μg bid, 500 μg bid or no treatment with inhaled FP for 6 months. Data were collected at baseline and at 1, 3 and 6 months after the start of treatment. HRQoL was assessed using the validated Spanish version of the *St. George's Respiratory Questionnaire*.
Results: The group administered FP 1000 μg daily showed significant improvement in dyspnea (1.03 [2.1]–1.24 [2.2] points; $P = 0.01-0.04$), sputum production ($P = 0.001$), days without cough ($P = 0.02$) and short-acting beta-2 agonists used ($P = 0.01$) from the first month of treatment, with no changes in pulmonary function, number or severity of exacerbations, or microbiological profile of the sputum. As a result, an improvement in HRQoL was seen in this group after 3 months of treatment (45.4 [14.2] vs. 40.5 [13.9]; $P = 0.01$).

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Conclusions: Inhalatory FP 500 μg bid is effective from the first month of treatment for controlling the symptoms of patients with steady-state bronchiectasis—thus ensuring a significant improvement in HRQoL.

Introduction

Bronchiectasis is a chronic airways disease characterized by progressive dilation and destruction of the bronchial tree.[1] As a result of the associated dysfunction of mucociliary clearance, a vicious circle is established involving persistent bacterial colonization, chronic inflammation of the bronchial mucosa, and progressive tissue destruction.[2] Studies of bronchial biopsies in patients with bronchiectasis have shown a significant acute and chronic inflammatory component involving mainly neutrophils and abundant CD_4+ and CD_8+T lymphocyte.[3,4] On the other hand, sputum analysis usually shows a large variety of cell secretion products (interleukin-8, interleukin-6 and tumor necrosis factor-α),[5,6] and enzymes such as elastases and neutrophil peroxidases.[7]

Bronchiectasis is associated with chronic and frequently purulent expectoration, multiple exacerbations, impaired lung function usually comprising chronic airflow obstruction with eventual bronchial hyperresponsiveness and the appearance, in advanced stages, of progressive dyspnea that can become disabling.[8] These alterations gradually worsen the health-related quality of life (HRQoL) of these patients.[9,10]

Very few studies have analyzed the effect of inhaled steroids upon the treatment of patients with steady-state bronchiectasis.[11–13] It seems to be well established that high doses of inhaled steroids afford some improvement of certain clinical parameters, without changes in lung function or in the number of exacerbations, among patients with bronchiectasis.[11] However, some important variables remain to be examined in this sense, such as the influence of different inhaled steroids doses (including their possible adverse effects) or the effect of this treatment upon patient HRQoL. This has led the Cochrane Collaboration[14] in an updated review of the subject, to stress the need for new studies in this field. We hypothesized that treatment with inhaled steroids in patients with steady-state bronchiectasis affords significant improvement in HRQoL fundamentally as a result of better clinical control.

The present study analyzes the effect of inhaled fluticasone propionate (FP) for 6 months upon the clinical, functional, microbiological and outcome parameters of patients with steady-state bronchiectasis not due to cystic fibrosis (CF), and its repercussions for patient HRQoL.

Materials and methods

Patient selection

The study initially included all patients with bronchiectasis affecting more than one pulmonary lobe or cystic bronchiectasis (localized or otherwise) not due to CF and diagnosed in our center between 1993 and June 2003. The patients were required to be clinically stable, i.e., free from acute exacerbations for at least 4 weeks. Exacerbation was defined as persistent (>24 h) deterioration of at least three respiratory symptoms (including cough, dyspnea, hemoptysis, increased sputum purulence or volume, and chest pain) with or without fever, radiographic deterioration, systemic involvement, or deterioration in chest signs.[13] The study excluded patients with possible asthma according to the definition of the *Global Initiative for Asthma* (*GINA*)[15]; patients with allergic bronchopulmonary aspergillosis according to previously described diagnostic criteria[16]; those unable to comply with the study protocol because of serious and unstable physical or psychiatric disorder; patients previously exposed to long-term oral steroid therapy or other immunosuppressants; and patients in whom prior inhaled steroid treatment (if any) could not be discontinued. Patients with suspected chronic obstructive pulmonary disease (COPD) were not excluded from the study, though we stratified randomization of the treatment groups according to smoking habit as measured in pack-years. The study was approved by the local ethics committee, and all patients gave informed consent to participation in the study.

Diagnosis of bronchiectasis

The diagnosis of bronchiectasis was established in all cases by high-resolution computed tomography (HRCT) of the chest with 1–1.5 mm sections every 10 mm and subsequent reconstruction following the criteria described by Naidich et al.[17] HRCT was

performed a maximum of 24 months prior to the start of the study. In the event diagnostic HRCT was performed at an earlier date, the exploration was repeated to update the diagnosis and the extent of bronchiectasis. To assess the presence and extent of bronchiectasis, the modified Bhalla score was used.[18] HRCT was interpreted by a radiologist and a clinician independently.

Study design

A prospective, randomized (stratified for prior smoking habit in pack-years), double-blind (only for effective doses) study was designed, comprising three groups of patients assigned to the following treatments for 6 months: no inhaled steroid treatment (Group 0 F), 250 μg bid (Group 500 F) or 500 μg bid (Group 1000 F) of inhaled FP (metered-dose inhaler) through a Volumatic® chamber for the purpose of analyzing the effect of treatment on various clinical, functional, microbiological and outcome variables, and its influence upon HRQoL. All patients were previously instructed by qualified staff on the proper use of the inhalers. The study was conducted on a double blind basis regarding the effective inhalatory steroid dose administered (500 vs. 1000 μg/day), but not as relates to the administration or not of steroid treatment (i.e., 0 vs. 500 or 1000 μg/day).

A complete clinical history was obtained in all patients, including information on their past medical history and details of their smoking habit. Patients who prior to starting the study were using long-term inhaled steroids for bronchiectasis were scheduled for three visits at 1-month intervals in the 3 months prior to randomization, in order to progressively reduce the steroid dose to discontinuation. On each visit, the dose of the previous visit was halved, discontinuing inhaled steroids on the third visit, controlling possible changes in patient clinical parameters or pulmonary function, and optimizing bronchodilator treatment in all cases. The patients were allowed to continue using their other regular treatments. After the inhaled steroids were completely removed, a 3-month washout period was completed before randomization was carried out.

Measurements

In all cases, baseline data collection started during the 6 months prior to randomization. In this period prospective information was obtained regarding the number of acute exacerbations, antibiotic use, cycles of oral steroids, and hospital admissions or visits to emergency rooms. During the randomization visit, the following tests were performed: (a) assessment of baseline dyspnea based on the baseline dyspnea index (BDI),[19] (b) retrieval of a symptoms in which the patients had recorded the number of days with cough or wheezing, and the number of inhalations of rescue short-acting β_2 agonists used in the month prior to randomization; (c) measurement of the mean amount of sputum produced daily (in ml). This was evaluated by instructing the patients to collect the amount of sputum during the 3 days prior to randomization in three graded sterile containers (one per day), and marking the amount reached each day on the container. Instructions were given to ensure that sputum collection was as correct as possible—the percentage saliva recorded being the lowest possible. The average of the three measurements was taken to be the valid sputum output; (d) assessment of HRQoL using the validated Spanish version of the *St. George's Respiratory Questionnaire* (SGRQ).[20]

On the other hand, three pairs of fresh sputum samples were collected in the 6 months prior to randomization, with 1 month between each pair of samples, for microbiological testing—including gram staining and culture in standard media or special media in the case of a clinically suspected specific microorganism. In valid sputum (<10 epithelial cells and >25 leukocytes/field),[21] chronic colonization was considered when the microorganism appeared as over 1×10^5 CFU/ml at least in three sputum samples corresponding to different visits outside an acute exacerbation period. During the days prior to randomization, the following pulmonary function measurements were made; forced spirometry measuring the forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC),[22] and the FEV_1 and FVC values 15 min after the inhalation of 200 μg of salbutamol. Total lung capacity (TLC) and residual volume (RV) were measured by the helium dilution technique and indexes of gas transfer were measured using a carbon monoxide single-breath test adjusted for alveolar volume (KCO); gas transfer results were adjusted for hemoglobin. All maneuvers were performed by qualified staff and at the same time in the morning.

After randomization, TLC, RV and KCO were analyzed again after 6 months of treatment. HRQoL assessment and the microbiological analysis of sputum were carried out after 3 and 6 months of treatment. Changes of over 4 points in the SGRQ were considered to be clinically significant.[23] The other tests described, and the appearance of side effects, were assessed at 1, 3, and 6 months in all

three groups of treatment. Dyspnea was assessed by the transition dyspnea index (TDI),[24] where changes of over 1 point were considered to be clinically significant.

Statistical analysis

All data were showed as the mean and standard deviation (SD) in the case of quantitative variables and as absolute values and percentages in the case of qualitative variables. The principal study variable was taken to be a clinically significant change ($\geqslant 4$ points) in SGRQ total score. We calculated that a sample size of 75 patients (25 per treatment group for comparing three repeated means) was required to detect a significant change in SGRQ total score with 80% power and 0.05 alpha-level test, assuming a maximum patient loss of 20% in the course of the study. The normality of all variables was verified by the Kolmogorov–Smirnov test. In the event of a non-normal distribution, log-transformation was carried out. This proved necessary for the variables referring to the number of acute exacerbations, cycles of steroids, oral antibiotics, or the number of visits to emergency rooms or hospital admissions. For the intergroup comparison of baseline data, a one-way analysis of variance (ANOVA) with Bonferroni correction was used in the case of quantitative variables, and the Friedman's test in the case of qualitative variables. For the intra- and intergroup comparison of variables during the study, a repeated-measure ANOVA was used. Calculations were also made of the minimum number needed to treat (NNT) to obtain a clinically significant change in the variables for which statistically significant changes were recorded ($P < 0.05$) with steroid treatment.[25]

Results

Patient demographics

Of the 132 patients initially included in the study, 39 were excluded prior to randomization. The most frequent cause of exclusion was the presence of a high clinical probability of bronchial asthma ($n = 23$). Ninety-three patients were therefore finally randomized. During the study, 7 additional patients were excluded (Fig. 1). Thus, 86 patients completed the study (28 in Group 0 F; 29 in Group 500 F and 29 in Group 1000 F). Table 1 shows the baseline characteristics of the three groups. Significant pre-randomization differences were only seen in the number of patients colonized by *Haemophilus influenzae (HI)*, which was lower in Group 500 F (7%, $P = 0.018$). Eighteen patients were using inhaled steroids prior to the start of the study. All but one of these individuals were able to completely discontinue inhalatory medication and completed the 3-month washout period prior to randomization. There were no significant differences among the three study groups in terms of the number of individuals using inhaled steroids prior to the start of the study.

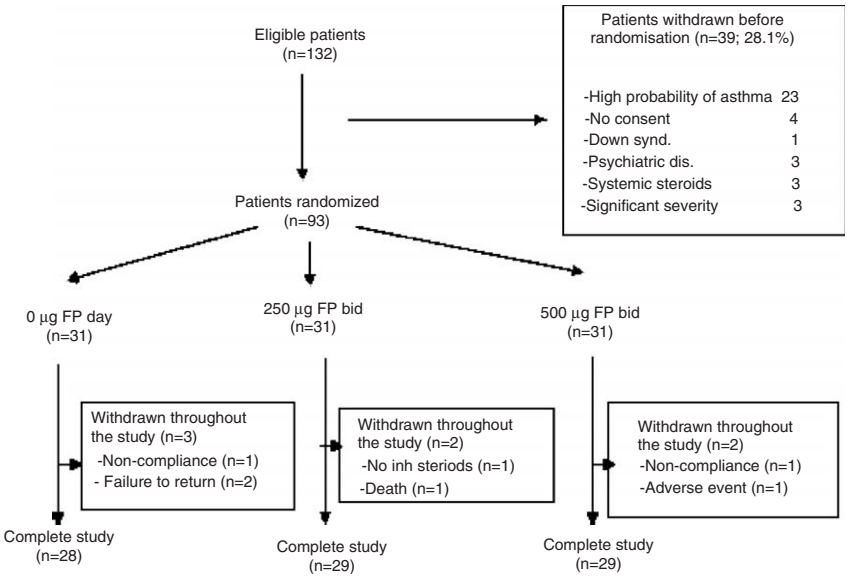

Figure 1 Profile of number of patients throughout the study.

Table 1 Demographics and baseline characteristics of the randomized patients who completed the study.

Variables	0 μg/d Fluti ($n = 28$)	500 μg/d Fluti ($n = 29$)	1000 μg/d Fluti ($n = 29$)
Age, yr	70.9 (6.1)	66.4 (12.6)	70.9 (6)
Gender (% males)	61	62	72
HRCT score	4.1 (2,3)	4.3 (2.2)	4.8 (2.5)
24-h sputum production (ml)	21.9 (23.1)	21.1 (24.8)	22.1 (14.7)
Smoking, pack-yr	37.3 (32)	35.1 (30.2)	36.8 (29.1)
BDI focal score	6.41 (2.6)	6.54 (2.6)	6.5 (3.1)
Short-acting β_2/week use	5.5 (4.1)	5.89 (4.5)	5 (4.7)
Long-acting β_2 (%)	68	76	72
Anticholinergics (%)	25	28	34
FEV_1, L	1405 (546)	1421 (567)	1384 (577)
FEV_1% predicted	62.3 (17.7)	61.7 (20.3)	59.8 (23,5)
FVC, L	2227 (719)	2357 (766)	2478 (727)
FVC, % predicted	74.8 (18.4)	78.9 (14.9)	79.3 (15.9)
Positive BDT (%)	21	17	17
Pseudomonas colonization (%)	21	17	24
H. influenzae colonization (%)	38	7*	21
No. of exacerbations	1.17 (1.3)	1.29 (1.7)	1.14 (1.1)
No. of hospital admissions	0.07 (0.3)	0.07 (0.3)	0.03 (0.2)
Total SGRQ score	45.5 (15.1)	45.2 (11.8)	45.5 (14.2)
Symptoms SGRQ score	45.3 (13.7)	45.6 (12.8)	45.3 (14.9)
Activity SGRQ score	51.6 (16.9)	51.8 (12.5)	53.2 (14.7)
Impact SGRQ score	40.3 (14.3)	38.5 (10.9)	40.8 (13.3)

Quantitative variables are tabulated as mean and standard deviation. Qualitative variable are tabulated as percentage. HRCT: High-resolution computed tomography; BDI: Basal dyspnea index; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; TBD; Bronchodilator test.

*$P = 0.018$ for 500 F vs. 0 F.

Changes in pulmonary function

There were no significant changes from baseline in any of the three treatment groups for any of the functional variables analyzed during the 6 months of the study. Reductions of 62 (181) and 39 (147) ml were found in FVC in Groups 0 F and 500 F, respectively, and an increase of 25 (104) ml in Group 1000 F at 6 months of treatment. Group 1000 F showed a non-significant improvement in FEV_1 that was more marked during the first month of treatment (+38 [145] ml) and reached +64 (154) ml vs. baseline after 6 months. No such improvement was seen in any of the other two groups (−11 [93] ml and −38 [107] ml for Groups 500 F and 0 F, respectively, at 6 months of treatment) (Fig. 2).

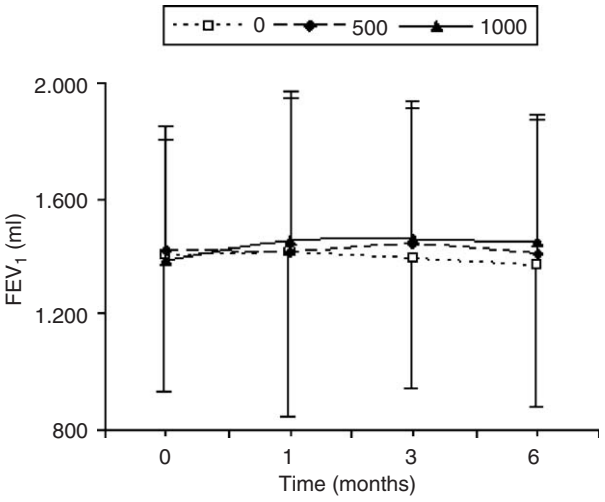

Figure 2 Changes in the absolute FEV_1 value in the three treatment groups along the 6 months of the study from baseline.

Dyspnea

All three treatment groups showed improvement in dyspnea (TDI), though clinical significance was only observed in Group 1000 F at 1 month of treatment (+1.03 [2.1] points; $P = 0.04$); this improvement persisted after 3 months (+1.28 [2.3] points; $P = 0.01$) and 6 months (+1.24 [2.2] points; $P = 0.02$) (Fig. 3). There were no statistically significant differences between Groups 1000 F and 500 F, though in the course of the study the latter group failed to reach the minimum improvement in dyspnea defining clinical significance (1 point). The

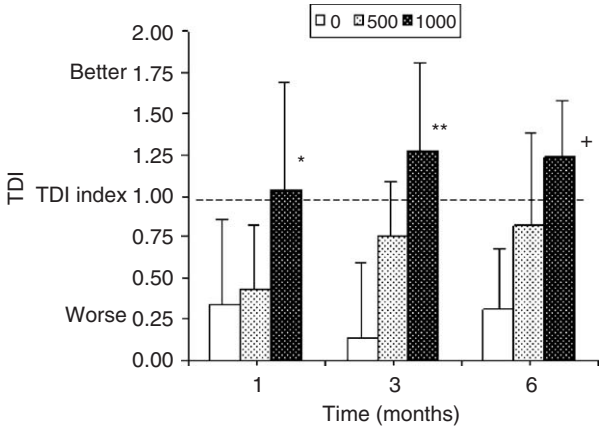

Figure 3 TDI values along the study in the three treatment groups. The discontinuous line is the threshold from which it is considered that there is a clinically significant improvement in dyspnea. Threshold of clinical significance. $^{*}P = 0.04$; $^{**}P = 0.01$; $^{+}P = 0.02$ for 1000 F vs. 0 F at 1, 3 and 6 months after randomization, respectively.

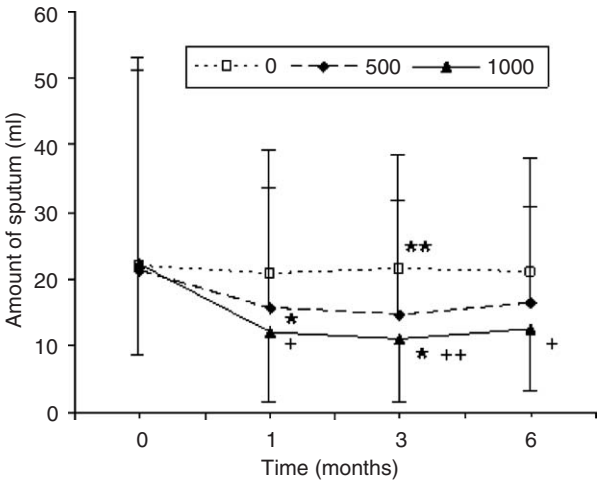

Figure 4 Changes in the amount of sputum produced daily in ml in the three treatment groups during the study. $^{*}P = 0.001$ for 1000 F vs. baseline values. $^{**}P = 0.02$ for 500 F vs. baseline values. $^{+}P = 0.04$ for 1000 F vs. 0 F at 1 and 6 months after randomization. $^{++}P = 0.01$ for 1000 F vs. 0 F at 3 months after randomization.

number (percentage) of patients improving over 1 point at 6 months of treatment was significantly greater in Group 1000 F than in Group 0 F (19 [65.5%] vs. 10 [34.5%], $P = 0.02$). The NNT with FP 1000 μg was four patients (95% CI: 2–25) to obtain at least a 1-unit improvement in TDI score after 6 months of treatment vs. the untreated group.

Daily sputum production

At 1 month of treatment, a significant reduction was observed in the volume of sputum from baseline in Group 1000 F (−9.7 [12.8] ml, $P = 0.001$) that persisted with minor variations during the 6 months of study. A significant reduction also occurred in Group 500 F from baseline at 3 months of treatment (−6.47 [12.5] ml; $P = 0.02$), though this effect decreased at 6 months (−4.4 [17.3] ml, $P = 0.21$) (Fig. 4). The intergroup study revealed a significant decrease in the amount of sputum produced in Group 1000 F vs. Group 0 F from the first month of treatment (−8.7 [11.3]; $P = 0.04$), and this situation persisted after both 3 (−10.7 [12.8]; $P = 0.01$) and 6 months (−8.3 [11.1]; $P = 0.04$). Fourteen patients treated with 1000 F (48.3%) had a reduction of over 50% in the amount of sputum at 6 months, as compared to 11 patients (37.9%) in Group 500 F ($P = 0.03$) and 3 (10.7%) in the untreated group ($P = 0.009$). The NNT was two patients (95% CI: 2–5) to obtain a reduction of 50% in the amount of sputum daily at 6 months of treatment with FP 1000 μg.

Days without cough and wheezing

Regular coughing (>50% of days) was recorded in 13 (46%), 12 (41%) and 13 (45%) of the patients in Groups 0 F, 500 F and 1000 F, respectively. A significant reduction in the number of patients with regular cough was only observed in Group 1000 F at 1 month of treatment (−17% [5 patients], $P = 0.02$)—an effect that persisted at 6 months (−24% [7 patients], $P = 0.01$). On the other hand, 9 [31%], 9 [32%] and 9 [31%] of the patients suffered regular wheezing in Groups 0 F, 500 F and 1000 F, respectively—without changes in the course of the study.

Need for short-acting β_2 agonists

The three treatment groups reduced their weekly need for short-acting β_2 agonists, though this reduction was only significant in Group 1000 F at 1 month of treatment vs. baseline (3.34 [3.4] vs. 5.03 [4.7]; $P = 0.01$)—a difference that persisted throughout the study (3.45 [3.5]; $P = 0.01$ and 2.72 [3.7]; $P = 0.01$ vs. baseline at 3 and 6 months, respectively)—and in Group 500 F at 6 months of treatment vs. baseline (3.67 [3.8] vs. 5.89 [4.5]; $P = 0.03$). After 6 months of treatment there were significant differences between 0 F and 1000 F (5.11 [3.8] vs. 2.72 [3.7]; $P = 0.01$). The differences between groups 500 F and 1000 F failed to reach statistical significance.

Number and severity of exacerbations

There were no significant differences in the number of acute exacerbations comparing those calculated 6 months before and after randomization (1.2 [1.1] vs. 1.4 [1.3]; $P = 0.89$ in Group 1000 F), or in the administration of cycles of antibiotics, cycles of oral steroids, visits to emergency rooms or hospital admissions for acute worsening of any respiratory condition in any of the three treatment groups.

Sputum microbiology

No significant changes were seen in the number (percentage) of chronic colonizations by HI (9 [32%], 4 [14%] and 8 [28%] in groups 0 F, 500 F, 1000 F, respectively, at 6 months) or *Pseudomonas aeruginosa* (PA) (5 [18%], 4 [14%] and 7 [24%] in groups 0 F, 500 F and 1000 F, respectively, at 6 months) in the three groups during the study vs. the pre-randomization percentages.

Adverse events

A global analysis showed adverse events to be more frequent in Group 1000 F vs. 500 F (19 vs. 7; $P = 0.04$). The most common problems were dry mouth (8 patients), local irritation ($n = 4$) and transient dysphonia ($n = 4$). Other side effects in Group 1000 F were aphthae ($n = 1$) and sneezing ($n = 1$). Oral candidiasis was only seen in two patients (one patient in Group 1000 F). All adverse events were mild and did not lead to treatment discontinuation, except for one patient in Group 1000 F who was removed from the study due to edema of the face after using an inhaled steroid. One death occurred in Group 500 F due to respiratory failure unrelated to inhalatory steroid use.

Changes in HRQoL

There were no significant pre-randomization differences among the three treatment groups as regards the total SGRQ score or scores of the three scales. There was clinically significant improvement ($\geqslant 4$ points) in total SGRQ score from baseline in Group 1000 F at 3 months of treatment (45.5 [14.2] vs. 40.5 [13.9], $P = 0.01$) that persisted at 6 months (Fig. 5A). Statistically significant improvement in this same group was observed at 3 and 6 months in the symptoms score (45.3 [14.9] vs. 37.1 [13.7] and 45.3 [14.9] vs. 35.3 [13.8], respectively, $P = 0.005$) (Fig. 5B) and at 6 months on the activity scale (53.2 [14.7] vs. 47.1 [14.1]; $P = 0.02$). There were no changes on the impact scale (40.8 [13.3] at baseline vs. 37.1 [12.7] at 6 months; $P = 0.11$). The number (percentage) of patients with clinically significant improvement in HRQoL was statistically greater in Group 1000 F at both three (2 [7.4%], 9 [31%] and 17 [58.6%] for groups 0 F, 500 F and 1000 F, respectively, $P = 0.003$) and 6 months (2 [7.4%], 10 [34.4%] and 15 [51.7%], respectively; $P = 0.009$) (Fig. 5C). The NNT was two patients (95% CI: 2–4) to obtain clinically significant improvement with treatment in the form of 1000 FP during 6 months.

Finally, an intent-to-treat analysis was carried out including 90 out of 93 randomized patients (29 in Group 0 F; 30 in Group 500 F, and 31 in Group 1000 F), since one patient died during the study and two failed to return for the first visit after randomization and could not be located. The results did not differ significantly in the analysis of any of the variables studied vs. the results obtained in the group of 86 patients that completed the study.

Discussion

In our series, treatment with inhaled FP 500 μg bid in patients with non-CF steady-state bronchiectasis led to significant and early improvement (as soon as after 1 month of treatment, and persisting for at least 6 months) in daily sputum production, dyspnea, days without cough, and number of doses of short-acting β_2 agonists required weekly. However, the parameters corresponding to microbiological colonization of sputum, pulmonary function and the number or severity of acute exacerbations did not change. These results afforded significant improvement in the HRQoL of these patients that persisted during the 6 months of treatment. Although the number of adverse events was globally greater in Group 1000 F, they were local and reversible.

In a recent study we found the parameters exerting the greatest effect upon HRQoL in patients with steady-state bronchiectasis to be dyspnea, airflow obstruction and daily sputum production.[10] In the present study, the significant clinical stability recorded in the group administered inhaled FP 1000 μg daily (attributable to minor improvement in dyspnea and significant reduction in daily sputum production) comprised clinically significant and sustained HRQoL improvement during the study. This parameter, which is fundamental given its multidimensionality in the efficacy of any therapeutic approach, had not been previously analyzed with this regard in patients with non-CF

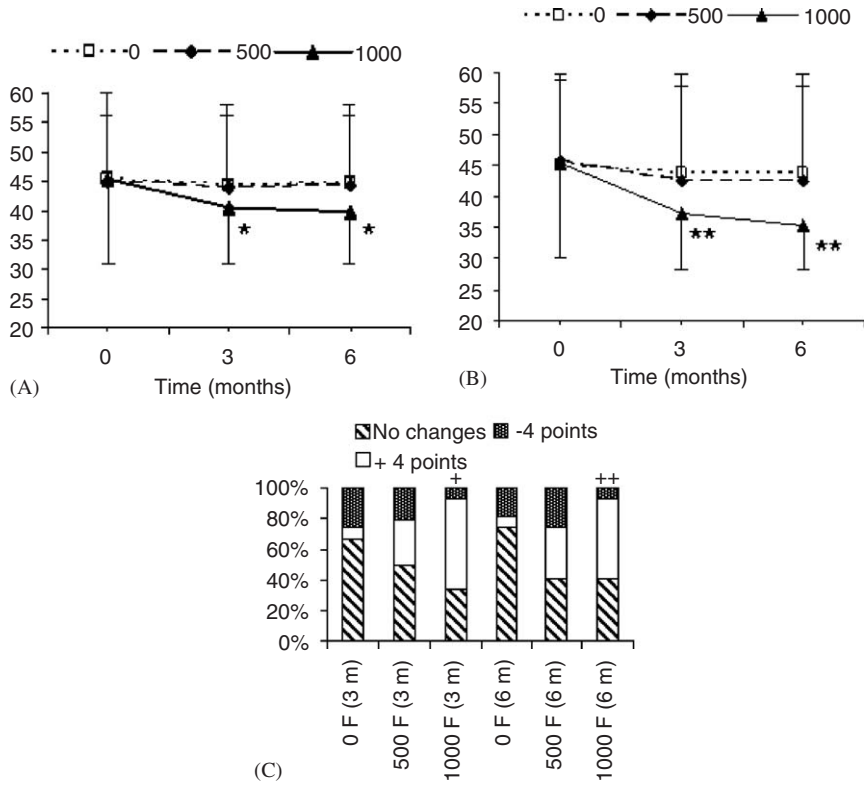

Figure 5 Changes in the HRQoL (SGRQ) during the study in the three treatment groups. (A) Changes in the total score. (B) Changes in the scale of symptoms. (C) Percentage of patients with significant changes (± 4 points). $^{*}P = 0.01$ for 1000 F vs. baseline values. $^{**}P = 0.005$ for 1000 F vs. baseline values. $^{+}P = 0.003$ for 1000 F vs. 500 F and 0 F at 3 months after randomization. $^{++}P = 0.009$ for 1000 F vs. 500 F and 0 F at 6 months after randomization.

bronchiectasis. In agreement with the clinical improvement observed, the questionnaire scale affording the greatest improvement and critically conditioning improvement in overall patient score was the symptoms scale. As regards the activity and impact scales of the questionnaire—more extensively determined by parameters such as dyspnea, functional variables or psychological factors—a statistically significant late improvement in the former was only obtained in the group treated with PF 1000 μg. However, the clinical significance of this improvement is difficult to evaluate, since no reference values are described for minimum relevant changes on this scale. According to our results, at least one out of every two patients (NNT) treated with 1000 PF showed significant improvements in HRQoL.

In two well-conducted studies, Tsang et al. reported that FP 1000 μg reduces 24-h sputum volume, leukocyte density and several inflammatory cytokines of sputum (Interleukin-8, leukotriene-B_4 and interleukin-1β), without modifying bacterial density in patients with bronchiectasis.[11,13] In this same sense, Elborn et al.[12] reported that 6-week treatment with high doses of beclomethasone produces significant reductions in sputum volume. Accordingly, in our study, the reduction in daily sputum production together with the improvement of dyspnea and the increase in days without cough implied that the group of patients treated with high-dose FP retained better clinical control—as supported by the significantly lesser need for short-acting β_2 agonists early from baseline. In contrast, treatment with FP 500 μg daily only yielded a moderate, late reduction in both daily sputum amount and the dose of short-acting β_2 agonist medication.

Similarly to COPD[26] and in some studies of patients with bronchiectasis,[11–13] treatment with high doses of inhaled steroids did not lead to significant improvement in the functional parameters. However, it must be noted that in our series, after 1 month of treatment with FP 1000 μg, FEV_1 increased 64 ml from baseline. This effect persisted after 6 months. However, we found a 38-ml reduction in the group without steroid treatment at 6 months. While not statistically significant, this observation could indicate slowing of the long-term decline in FEV_1 among treated patients, supported by the fact that most patients

with bronchiectasis have been suggested to show a mean annual loss of 50 ml in FEV_1.[8] Longer term studies would be needed to confirm this, however.

Another conclusion that can be drawn from our study, in line with the recent observations of Tsang et al.[13] is that inhaled steroids do not appear to reduce the number of acute exacerbations in these patients—though no increase is seen in chronic colonization by potentially pathogenic organisms such as PA or HI. No changes were seen in the severity of acute exacerbations considering the lack of changes in the number of hospital admissions, visits to emergency rooms and the number of cycles of antibiotics or oral steroids prescribed in the three treatment groups. In this context, the behavior of bronchiectasis is different from that seen in asthma and severe COPD—these being disorders where a reduction in the number of exacerbations has been described with inhaled steroids therapy.[26,27] It is likely that the explanation for this discrepancy is the inability of steroids to eradicate organisms more frequently causing acute exacerbations in these patients, such as PA or HI which are strongly attached to a structurally altered bronchial mucosa—causing chronic inflammation that proves difficult to resolve without eliminating the organism.[28]

It is important to mention that special care was taken to exclude patients with suspected bronchial asthma according to the definition of the GINA, since corticosteroids are known to be the most effective therapy available for asthma.[15] However, we decided not to exclude patients with COPD, due to the great difficulty sometimes found in differentiating smokers with bronchiectasis who moreover also present COPD from those who do not have COPD. In any case, since some studies have shown a certain positive effect of inhaled steroids upon some clinical and functional parameters in patients with advanced COPD,[10,11] randomization of treatment was stratified for prior smoking habit as measured in pack-years.[26,29]

Our study has a number of limitations that should be commented. Firstly, no placebo group was included, due to the lack of availability of placebo in our center. In an attempt to partly make up for this deficiency, we introduced an untreated patient group and a group with an intermediate dose to be used as control for assessing efficacy over time of the higher daily drug dose (PF 1000 μg). In addition, the study was conducted on a partially double-blind basis, since both the patient and the investigators were aware of whether or not inhalatory steroid treatment had been prescribed, but they did not know the effective doses involved (500 vs. 1000 μg/day).

In conclusion, we consider that despite a lack of improvement in pulmonary function and the number or severity of acute exacerbations, patients with non-CF steady-state bronchiectasis could benefit from treatment with inhaled FP 500 μg bid, due to the significant reduction in the amount of sputum produced, the improvement in dyspnea, and the increase in days without cough—thus allowing for lesser use of rescue medication and clinically significant improvement in HRQoL.

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