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Towards clinical phenotyping of COPD : effects of inhaled corticosteroide in the GLUCOLD study

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Chapter 5

**Effect of fluticasone with and without
salmeterol on pulmonary outcomes
in chronic obstructive pulmonary disease:
a randomized, controlled trial**

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Abstract

Background: Inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABAs) are used to treat moderate to severe chronic obstructive pulmonary disease (COPD).

Objective: To determine whether long-term ICS therapy, with or without LABAs, reduces inflammation and improves pulmonary function in COPD.

Design: Randomised, placebo-controlled trial. (ClinicalTrials.gov registration number: NCT00158847)

Setting: 2 university medical centers in The Netherlands.

Patients: 114 steroid-naïve current or former smokers with moderate to severe COPD.

Measurements: Cell counts in bronchial biopsies and sputum (primary outcome); methacholine responsiveness at baseline, 6 and 30 months; and clinical outcomes every 3 months.

Intervention: Random assignment by minimization method to receive fluticasone propionate, 500 μg twice daily, for 6 months ($n=31$) or 30 months ($n=26$); fluticasone, 500 μg twice daily, and salmeterol, 50 μg twice daily, for 30 months (single inhaler; $n=28$); or placebo twice daily ($n=29$).

Results: 101 Patients were greater than 70% adherent to therapy. Fluticasone therapy decreased counts of mucosal CD3⁺ cells (-55% [95% CI, -74% to -22%]; $P = 0.004$), CD4⁺ cells (-78% [CI, -88 to -60%]; $P < 0.001$), CD8⁺ cells (-57% [CI, -77% to -18%]; $P = 0.010$), and mast cells (-38% [CI, -60% to -2%]; $P = 0.039$) and reduced hyperresponsiveness ($P = 0.036$) versus placebo at 6 months, with effects maintained after 30 months. Fluticasone therapy for 30 months reduced mast cell count and increased eosinophil count and percentage of intact epithelium, with accompanying reductions in sputum neutrophil, macrophage, and lymphocyte counts and improvements in FEV₁ decline, dyspnea, and quality of life. Reductions in inflammatory cells correlated with clinical improvements. Discontinuing fluticasone therapy at 6 months increased counts of CD3⁺ cells (120% [CI, 24% to 289%]; $P = 0.007$), mast cells (218% [CI, 99% to 407%]; $P < 0.001$), and

plasma cells (118% [CI, 9% to 336%]); $P = 0.028$) and worsened clinical outcome. Adding salmeterol improved FEV₁ level.

Limitations: The study was not designed to evaluate clinical outcomes. Measurement of primary outcome was not available for 24% of patients at 30 months.

Conclusions: ICS therapy decreases inflammation and can attenuate decline in lung function in steroid-naïve patients with moderate to severe COPD. Adding LABAs does not enhance these effects.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decrease in lung function, accompanied by worsening respiratory symptoms and health status [1]. These clinical features are associated with airway inflammation (such as that resulting from neutrophils, macrophages, lymphocytes, and mast cells) [2-5] and alterations of the bronchial epithelium (such as that resulting from squamous cell metaplasia or goblet and basal cell hyperplasia) [6].

Current guidelines [1] recommend treating patients who have severe COPD and frequent exacerbations with inhaled corticosteroids (ICSs) and adding long-acting β_2 -agonists (LABAs) for Patients with moderate to severe COPD. Regular ICS treatment leads to clinical benefits in terms of symptoms, exacerbation rates, and initial improvements in FEV₁ [7-10]. However, withdrawal of ICS treatment results in deterioration of clinical outcome [11;12]. Combining a LABA with an ICS provides additional clinical improvements [13;14]. A recent analysis of the TORCH (Towards a Revolution in COPD Health) study suggests that prolonged therapy with ICS and LABA attenuates FEV₁ decline in COPD [15], in contrast to previous studies [13;14;16-19].

94 The clinical benefits of ICS therapy for COPD, with or without a LABA, may be at least partially mediated its anti-inflammatory efficacy. Short-term treatment of COPD (2-3 months) with ICS reduced the number of bronchial mast cells but not CD8⁺ cells, neutrophils, or macrophages [20;21]. Combination therapy with ICS and LABAs for 3 months provided more anti-inflammatory effects than ICS monotherapy by reducing bronchial CD8⁺ cells and macrophages [22]. No long-term anti-inflammatory effects have been reported for these interventions. Our goal was to link pathological and clinical efficacy during 30-month treatment.

We hypothesized that:

- 1) long-term maintenance therapy with ICS provides anti-inflammatory effects (primary outcome) in the airways of patients with COPD;
- 2) such effects are associated with clinical improvements;
- 3) discontinuing ICS therapy induces a flare-up of inflammation and clinical deterioration; and
- 4) adding a LABA to ICS therapy provides no further anti-inflammatory effects.

Methods

Our study is investigator-initiated, with a double-blind, parallel, 4-group, placebo-controlled, randomised design.

Setting and participants

The GLUCOLD (Groningen Leiden Universities Chronic Obstructive Lung Disease) project [23] enrolled patients with COPD who were aged 45 to 75 years, were current or former smokers, had smoked for 10 or more pack-years, and had lung function levels compatible with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II and III [1]. Exclusion criteria were asthma and receipt of ICS within 6 months before random assignment. We determined the presence of asthma on the basis of a physician's diagnosis or self-reported history, symptoms, treatment, or diagnosis of asthma. Patients were clinically stable and were allowed to continue taking short-acting bronchodilators. We determined smoking status on the basis of self-reports and gave standard clinical advice to quit smoking in accordance with Dutch national guidelines. We recruited almost all patients from family practices by electronically selecting patients aged 45 to 75 years who did not have an International Classification of Primary Care code for asthma (R96). Their general practitioner sent them a letter asking for participation in research. A telephone interview revealed 4617 potentially eligible patients, who received spirometry. In addition, we recruited patients by advertising in local newspapers. We performed chest radiography and electrocardiography to rule out important comorbid conditions. Recruitment and follow-up was between 2000 and 2007. Both centers' ethics committees approved the study, and all patients provided written informed consent.

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Random assignment and interventions

We randomly assigned patients to receive 1 of 4 regimens: fluticasone propionate, 500 µg twice daily, for the first 6 months followed by placebo, twice daily, for 24 months; fluticasone, 500 µg twice daily, for 30 months; fluticasone, 500 µg twice daily, and salmeterol, 50 µg twice daily, in a single inhaler for 30 months; or placebo, twice daily, for 30 months. Study medications were individually numbered, and we used Diskus dry-powder inhalers (GlaxoSmithKline, Zeist, The Netherlands) with 60 doses per inhaler; all active treatment medication and placebo were identical in appearance. The placebo consisted of lactose monohydrate (also included in other treatment groups). At entry, an independent randomisation center provided patient

and medication numbers by using a minimization procedure that balanced treatment groups for center, sex, smoking status, FEV₁/IVC (<60% or ≥ 60%), and methacholine PC₂₀ (the provocative concentration of methacholine that causes a 20% decrease in FEV₁) (<2 mg/mL or ≥ 2 mg/mL).

Outcomes and Measurements

Our predefined primary outcome was inflammatory cell counts in bronchial biopsies and induced sputum. We performed fiberoptic bronchoscopy, biopsy processing, and quantification as described elsewhere [24]. We stained paraffin-embedded biopsy sections with Periodic acid-Schiff/Alcian blue to identify goblet cells, epithelial intactness, and squamous metaplasia as described elsewhere [25]. We performed immunohistochemistry by using specific antibodies against T lymphocytes (CD3, CD4, and CD8), macrophages (CD68), neutrophil elastase, mast cell tryptase (AA1), eosinophils (EG2), plasma cells (CD138), and proliferating cells (Ki-67). We expressed subepithelial cells as number of cells per 10⁻⁷ m² by fully automated image analysis [26]. We used the full sample method [23] to perform sputum induction.

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Secondary outcomes included postbronchodilator spirometry and hyperresponsiveness to methacholine PC₂₀, assessed by using standardized procedures [23], dyspnea score by the modified Medical Research Council (MRC) dyspnea scale (range, 1 to 5); and health status by the St. George's Respiratory Questionnaire (SGRQ) (range, 0 to 100; 100 = maximum disability) [27] and Clinical COPD Questionnaire (CCQ) (range, 0 to 6; 6 = worst) [28].

Follow-up Procedures

We measured symptoms, health status, self-reported smoking status, medication adherence, and spirometry every 3 months. We checked adherence by counting the doses on the inhalers. We performed bronchoscopy, sputum induction, and methacholine challenge at baseline and at 6 and 30 months.

Statistical analysis

We based our sample size on the latest data released in 2002 [29] regarding the standard deviation (0.77) of the fluticasone-induced short-term change in submucosal CD8 cell count in patients with COPD. A 2-fold difference in change from baseline to 6 months and from 6 to 30 months in the fluticasone group versus placebo should be detectable with 80% power with 20 patients per treatment group. Because this was an efficacy trial, per-protocol analysis included all available data from randomly assigned patients who adhered to

their therapy regimen (using $\geq 70\%$ of the prescribed dose), including data from patients who did not complete follow-up.

We used linear mixed-effects models with a random intercept at the patient level to analyze the data and assumed that data were missing at random. We used STATA, version 9.0 (StataCorp, College Station, Texas) for analysis. The linear mixed models included the main effect of treatment (3 indicators), the main effect of time (2 indicators), and the interaction of treatment and time. For outcomes with 3-month measurements, we replaced the time effect with terms that allowed a shift or linear change in the average outcome during the first 6 months and a subsequent linear change in the average outcome after 6 months. Because of the considerable number of model parameters and the sample size, we did not include center, age, or sex as covariates in the baseline model. We performed a post hoc analysis to adjust for smoking status at baseline and during the study. We present the effects as adjusted means in the figures and as percentage of change in estimates, CIs, and *P* values in the text.

We analyzed correlations between statistically significant treatment effects on inflammatory outcomes and lung function by using the Spearman correlation coefficient (*R*s). Data are presented as means (SDs) or medians (interquartile ranges). We considered 2-sided *P* values less than 0.05 to be statistically significant.

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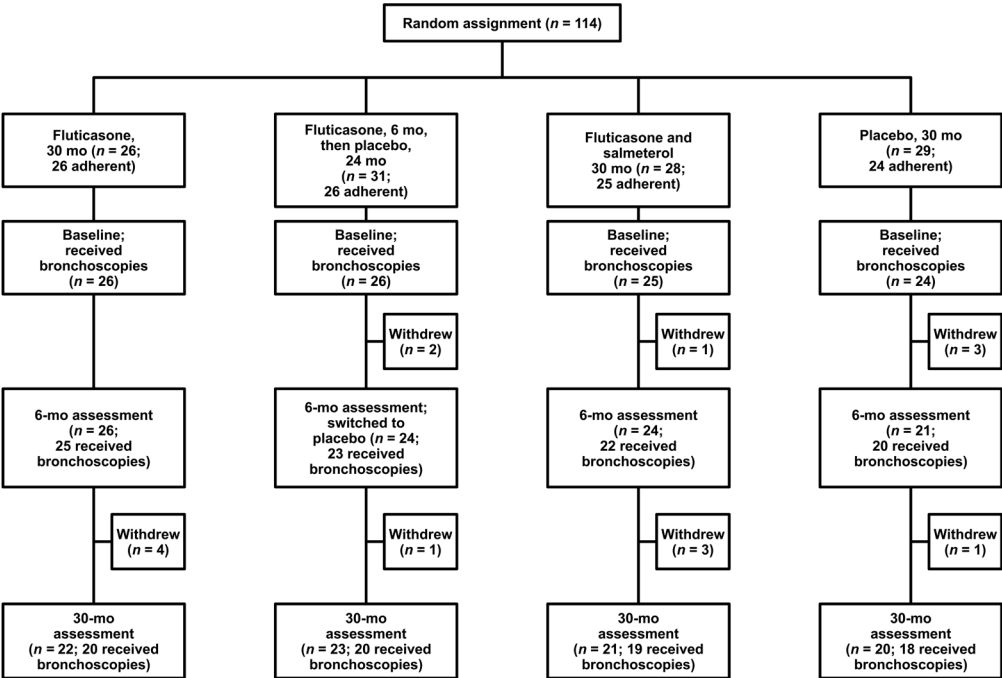
Role of the funding source

This was an investigator-initiated trial. The study was funded by the Netherlands Organization for Scientific Research, Netherlands Asthma Foundation, GlaxoSmithKline of The Netherlands, University Medical Center Groningen, and Leiden University Medical Center. The funding sources had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

Results

Of the 114 randomly assigned patients, we analyzed 101 adherent patients (**Figure 1**). Mean postbronchodilator FEV₁ was 63% predicted (SD, 9%) (91 patients were GOLD stage II and 10 were GOLD stage III) and geometric mean methacholine PC₂₀ was 0.6 mg/mL (SD, 2.6 doubling dose). Seven patients had ever received a short course of corticosteroids and only 5 had ever received ICS maintenance therapy.

Figure 1. Study flow diagram



Total number of patients randomised and compliant (>70% medication use) per treatment group. At each stage of the study (0, 6 and 30 months) the numbers are listed of those who underwent bronchoscopy amongst the number of patients remaining in the study. Definition of abbreviations: n = number.

Baseline patient characteristics were similar among the 4 treatment groups (Table 1). Sputum and biopsy inflammatory cells counts did not differ.

The amount of missing data, including missing data due to dropouts, for each study measure were 12% for FEV₁, 13.9% for methacholine PC₂₀, 12.5% for MRC score, 13.9% for SGRQ score, 14.7% for CCQ score, 12.5% for bronchial inflammatory cells, 14.2% for epithelial features, and 14.2% sputum cells.

Short-term therapy with ICS

Fluticasone therapy decreased counts of bronchial CD3⁺ cells (-55% [CI, -74% to -22%]; *P* = 0.004), CD4⁺ cells (-78% [CI, -88% to -60%]; *P* < 0.001), CD8⁺ cells (-57% [CI, -77% to -18%]; *P* = 0.010), and mast cells (-38% [CI, -60% to -2%]; *P* = 0.039) at 6 months compared with placebo (Figure 2 and Table 2). This was accompanied by an increase in methacholine PC₂₀ (1.5 doubling dose [CI, 0.1 to 3.0]; *P* = 0.036) (Figure 3, B) and CCQ mental score (0.2 point [CI, 0.01 to 0.4 points]; *P* = 0.037) compared with placebo. We found no other

Table 1. Patient characteristics at baseline *

Characteristics	Placebo, 30 mo	Fluticasone 6 mo, Then Placebo, 24 mo	Fluticasone, 30 mo	Fluticasone plus salmeterol, 30 mo	P value [†]
Patients, n	24	26	26	25	
Clinical					
Men/women, n/n	20/4	22/4	23/3	22/3	0.94
Age, y	59 (8)	64 (7)	62 (8)	62 (8)	0.31
Current smoker/ not current smoker, n/n	17/7	14/12	16/10	17/8	0.61
Median smoking history (range), pack-years	42 (34-54)	41 (29-57)	44 (31-55)	47 (31-56)	0.62
Lung Function					
Prebronchodilator FEV ₁ , % predicted	54.1 (8.3)	56.8 (11)	56.6 (9.9)	55.0 (11)	0.742
Postbronchodilator FEV ₁ , % predicted	61 (8.3)	65 (8.6)	64 (9.1)	61 (9.4)	0.41
Change in FEV ₁ , % predicted [‡]	7.1 (4.5)	7.3 (5.3)	7.1 (4.0)	6.2 (6.3)	0.87
Postbronchodilator FEV ₁ /IVC, %	47 (9.0)	51 (8.3)	49 (9.0)	46 (8.4)	0.157
Geometric mean methacholine PC ₂₀ , mg/mL [§]	0.7 (2.0)	0.7 (3.2)	0.4 (2.4)	0.7 (2.7)	0.64
K _{CO} , % predicted	65 (19)	79 (29)	77 (22)	74 (27)	0.188
Symptoms and health status					
MRC dyspnea score	2.7 (0.8)	2.5 (0.6)	2.6 (0.6)	2.9 (1.0)	0.53
SGRQ total score [¶]	33.5 (18.5)	25.7 (15.2)	32.9 (10.9)	28.1 (13.2)	0.27
CCQ total score ^{**}	1.77 (1.3)	1.16 (0.6)	1.26 (0.6)	1.43 (0.7)	0.35

CCQ = Clinical COPD [chronic obstructive pulmonary disease] Questionnaire; IVC = inspiratory vital capacity; K_{CO} = transfer factor for carbon-monoxide; methacholine PC₂₀ = provocative concentration of methacholine that causes a 20% decrease in FEV₁; MRC = Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.

* Values are means (SDs) unless otherwise indicated.

[†] By analysis of variance or Kruskal-Wallis tests between groups.

[‡] Reversibility in FEV₁ by 400-µg inhaled salbutamol.

[§] Methacholine PC₂₀ values are expressed as mean doubling doses.

^{||} Range of 1 to 5 (a higher score indicates more dyspnea).

[¶] Range of 0 (best) to 100 (worst).

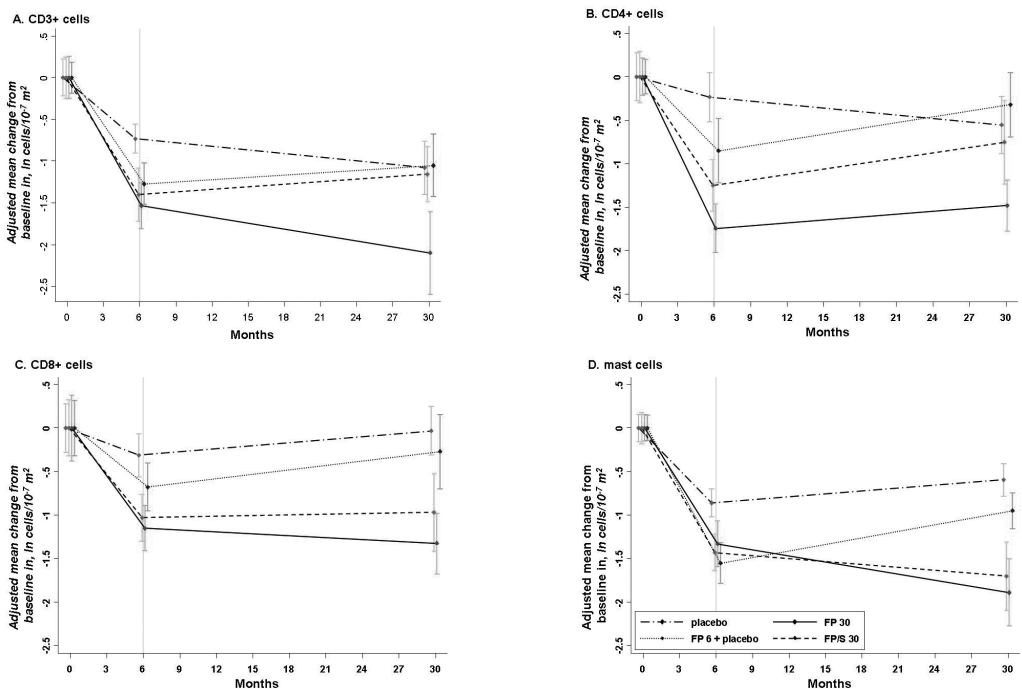
^{**} Range of 0 (best) to 6 (worst).

statistically significant effects of 6 months of fluticasone therapy. The change in FEV₁ after 6 months did not significantly differ between patients who were randomly assigned to continue fluticasone therapy and those assigned to switch to placebo.

Long-term continuation of ICS therapy

Continuing fluticasone therapy from 6 to 30 months maintained the reduction in CD3⁺, CD4⁺ and CD8⁺ cell counts (Figure 2 and Table 2) after 30 months, compared with placebo. This was accompanied by a further -56% change in mast cell count (CI, -73% to -29%; $P = 0.001$), a 125% increase in eosinophil count (CI, 2% to 399%; $P = 0.046$), and a 101% increase in the percentage of intact epithelium in bronchial biopsies (CI, 10% to 268%; $P = 0.024$) after 30 months (Figure 2 and Tables 2 and 4). In addition, the 30-month fluticasone group had lower counts of sputum neutrophils (-58% [CI, -82% to -1%]; $P = 0.047$), macrophages (-57% [CI, -81% to -3%]; $P = 0.041$), and lymphocytes

Figure 2. Pathological outcomes



Adjusted mean change in log-transformed bronchial cell numbers ($/10^{-7} \text{ m}^2$ lamina propria) over time during treatment with fluticasone (500 μg bid) for 30 months (FP30), fluticasone (500 μg bid) for 6 months (FP6), the combination of fluticasone/salmeterol (500/50 μg bid) for 30 months (FP/S) and placebo for 30 months in patients with COPD. Error bars represent 95% confidence intervals (CI). Data of bronchial CD3⁺ cells (2A), CD4⁺ cells (2B), CD8⁺ cells (2C), and mast cells (2D) are presented.

Table 2. Bronchial inflammatory cell counts at baseline and after 6 and 30 months*

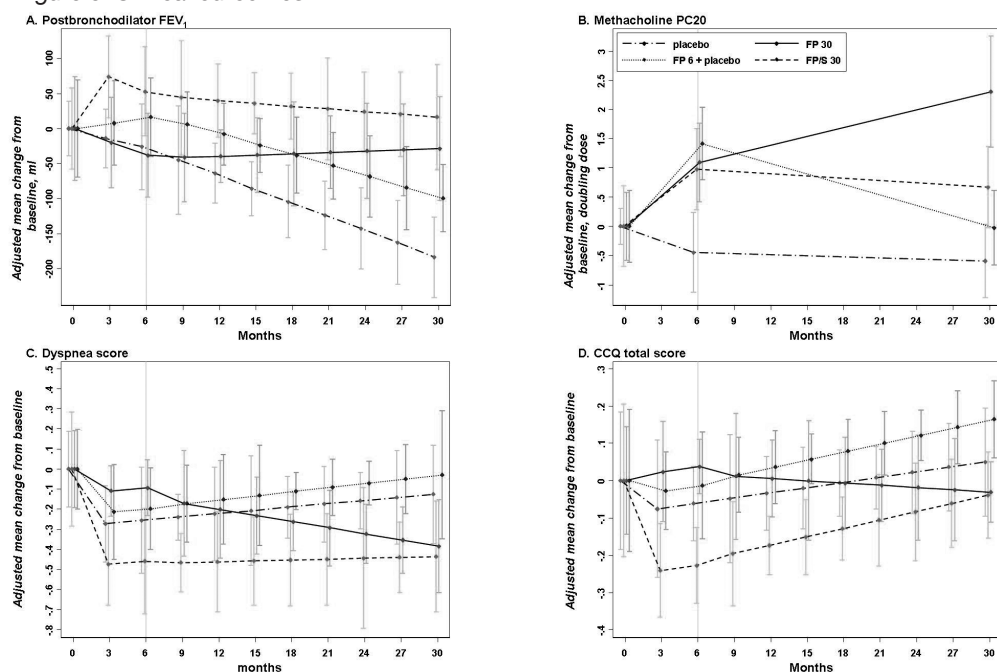
	Placebo, 30 mo			Fluticasone, 6 mo, then Placebo, 24 mo			Fluticasone, 30 mo			Fluticasone Plus Salmeterol, 30 mo		
	Baseline	6 mo	30 mo	Baseline	6 mo	30 mo	Baseline	6 mo	30 mo	Baseline	6 mo	30 mo
Patients, n	24	20	18	26	23	20	25	24	19	25	22	19
CD3 ⁺ cells	135 (76-197)	57 (37-84)	50 (24-79)	111 (69-180)	28 (21-45)	38 (19-89)	124 (63-192)	21 (16-33)	12 (5.5-38)	118 (74-191)	35 (17-54)	36 (15-53)
CD4 ⁺ cells	44 (21-66)	33 (18-67)	24 (11-42)	34 (24-67)	11 (6.5-19)	27 (12-57)	68 (43-100)	10 (6.0-19)	22 (6.5-26)	48 (26-82)	11 (6.9-25)	15 (11-57)
CD8 ⁺ cells	19 (10-33)	14 (9.0-23)	22 (12-33)	17 (6.9-29)	5.5 (3.0-9.0)	11 (4.3-19)	23 (11-41)	6.8 (3.3-9.5)	4.0 (2.0-9.5)	23 (16-52)	8.8 (6.3-19)	7.5 (4.0-24)
Neutrophils	4.0 (2.1-8.0)	3.0 (1.5-10)	5.3 (2.9-15)	5.0 (1.5-9.0)	7.0 (3.0-11)	9.8 (5.6-22)	2.5 (1.5-5.0)	5.5 (2.6-12)	13 (8.5-24)	5.0 (3.0-8.0)	6.3 (3.0-18)	7.5 (4.0-24)
Eosinophils	1.0 (0.5-5.8)	0.5 (0-2.2)	1.0 (0.4-3.4)	2.0 (0.5-7.5)	0.5 (0-1.0)	5.5 (1.1-11)	1.5 (0.5-3.3)	0.5 (0-1.4)	2.5 (1.0-8.5)	1.5 (0.5-2.5)	0.3 (0-3.3)	1.0 (0-5.0)
Plasma cells	7.8 (3.5-17)	2.0 (1.5-11)	5.5 (2.0-12)	11 (7.4-14)	2.0 (1.0-3.0)	6.3 (1.6-13)	8.0 (2.8-15)	2.0 (0.6-3.4)	1.0 (1.0-3.0)	6.5 (4.0-18)	1.3 (0.4-2.5)	4.0 (1.0-7.5)
Macrophages	8.3 (4.1-10)	5.3 (2.6-12)	4.0 (2.9-15)	9.3 (4.5-12)	3.5 (2.0-7.5)	5.3 (2.3-14)	10 (5.0-23)	4.0 (2.5-7.9)	3.0 (0.5-8.5)	9.5 (5.5-12)	4.8 (1.9-12)	4.0 (0.5-21)
Mast cells	24 (17-32)	11 (8.5-13)	14 (9.6-18)	31 (23-41)	6.0 (3.0-9.0)	12 (7.5-16)	22 (16-34)	8.0 (3.0-10)	2.5 (0.5-4.5)	26 (17-32)	7.0 (4.4-8.8)	5.0 (1.5-10)

* Cell counts are expressed as medians (25th-75th percentiles) count/10⁻⁷ m² of subepithelium

(-52% [CI, -76% to -5%]; $P = 0.035$) at 30 months than did the placebo group (Table 3).

The rates of FEV₁ decline from 6 to 30 months were -79 mL/y (CI, -112 to -46 mL/y) for the placebo group, -62 mL/y (CI, -93 to -31 mL/y) for the 6-month fluticasone group, 7.3 mL/y (CI, -21 to 35 mL/y) for the 30-month fluticasone group, and -16 mL/y (CI, -46 to 15 mL/y) for 30-month fluticasone and salmeterol group. Fluticasone significantly diminished annual FEV₁ decline over the last 2 years of the study compared with placebo (difference, 86 mL/y [CI, 43 to 129 mL/y]; $P < 0.001$) (Figure 3, A). The improvement in methacholine PC₂₀ by fluticasone compared with placebo that we observed during the first 6 months was maintained during the following 2 years (Figure 3, B). In addition, maintaining fluticasone therapy reduced dyspnea scores more than placebo over the last 2 years of the study (-0.2 point/y [CI, -0.3 to -0.06 point/y]; $P = 0.003$) (Figure 3, C), and significantly improved SGRQ activity score (-3.1 points/y [CI, -5.5 to -0.7 points/y]; $P = 0.012$) and CCQ total score (-0.1 point/y [CI, -0.2 to -0.01 points/y]; $P = 0.036$), symptom score (-0.1 points/y [CI, -0.3 to -0.02 points/y]; $P = 0.026$), and functional score (-0.1 points/y [CI, -0.2 to -0.01]; $P = 0.027$) (Figure 3, D).

Figure 3. Clinical outcomes



Adjusted mean change $\pm$ 95% CI over time during treatment with fluticasone (500 μ g bid) for 30 months (FP 30), fluticasone (500 μ g bid) for 6 months (FP 6), followed by placebo (as indicated by the vertical line), the combination of fluticasone/salmeterol (500/50 μ g bid) for 30 months (FP/S 30) and placebo (bid), in patients with moderately severe COPD. Changes in PC₂₀ are expressed as mean doubling doses. Data are presented for forced expiratory volume in one second (FEV₁) (3A), log-transformed provocation concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) (3B), Medical Research Council dyspnea score (3C) and Clinical COPD Questionnaire (CCQ) (3D).

Discontinuation of ICS therapy

Discontinuing fluticasone therapy after 6 months increased CD3⁺ cell count by 120% (CI, 24% to 289%; $P = 0.007$), mast cell count by 218% (CI, 99% to 407%; $P < 0.001$), and plasma cell count by 118% (CI, 9% to 336%; $P = 0.028$) at 30 months versus continuing therapy (Figure 2 and Table 2). Bronchial epithelial parameters and sputum inflammatory cells did not change significantly (Tables 3 and 4).

Discontinuing fluticasone therapy after 6 months worsened subsequent FEV₁ decline compared with continuing therapy during the last 2 years of follow-up (difference in slope, -70 mL/y [CI, -111 to -28 mL/y]; $P = 0.001$) (Figure 3, A), with an accompanying deterioration in methacholine PC₂₀ (-2.6 doubling dose [CI, -4.1 to -1.2 doubling dose]; $P < 0.001$) (Figure 3, B). Stopping fluticasone therapy also worsened dyspnea scores by 0.2 points/y (CI, 0.08 to 0.3 points/y; $P = 0.001$) (Figure 3, C), SGRQ total score by 1.7 points/y (CI, 0.19 to 3.2

points/y; $P = 0.028$) and activity score by 2.9 points/y (CI, 0.6 to 5.3 points/y; $P = 0.015$), and CCQ total score by 0.1 point/y (CI, 0.04 to 0.2 points/y; $P = 0.003$) and symptom score by 0.2 points/y (CI, 0.1 to 0.3 points/y; $P < 0.001$), compared with continuing therapy (data not shown).

Addition of LABAs to ICS therapy

At 6 months, combination treatment provided no additional anti-inflammatory effects compared with fluticasone alone; however, at 30 months, CD3⁺ cell count had increased by 126% (CI, 27% to 303%; $P = 0.006$) and plasma cell count by 144% (CI, 21% to 393%; $P = 0.013$) (Figure 2 and Table 2), and eosinophils in bronchial biopsies had changed by -55% (CI, -79% to -1%; $P = 0.047$). Salmeterol had no additional effect on bronchial epithelial parameters or sputum inflammatory cells (Table 3 and 4).

At 6 months, combination therapy increased postbronchodilator FEV₁ (96 mL [CI, 16 to 176 mL]; $P = 0.018$) (Figure 3, A) and improved dyspnea scores (-0.4 points [CI, -0.7 to -0.04 points]; $P = 0.027$) (Figure 3, C) more than fluticasone alone. Improved FEV₁ was maintained during prolonged combination therapy without further alteration of FEV₁ decline, compared with fluticasone alone, but the dyspnea score increased after 30 months (0.1 points/y [CI, 0.01 to 0.3 points/y]; $P = 0.029$). During the first 6 months, combination therapy resulted in a change of -0.3 points (CI, -0.5 to -0.07 points; $P = 0.007$) in CCQ total score, -0.3 points (CI, -0.6 to -0.04; $P = 0.028$) in symptom score, and -0.3 points (CI, -0.6 to -0.08 points; $P = 0.008$) in functional score (Figure 3, D). The minimal clinically important difference of 0.4 was not reached [30]. During the subsequent 24 months, combination therapy did significantly worse than

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Table 3. Sputum inflammatory cell counts at baseline and after 6 and 30 months*

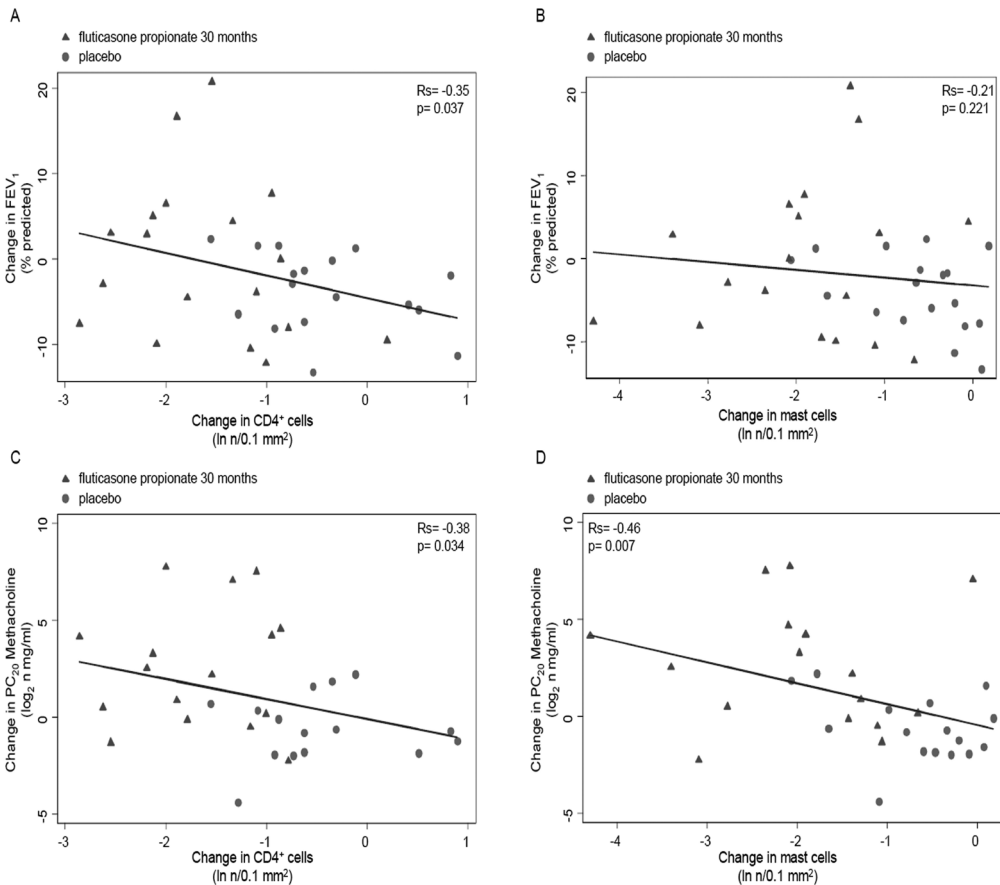
	Placebo, 30 mo			Fluticasone, 6 mo, Then Placebo, 24 mo			Fluticasone, 30 mo			Fluticasone Plus Salmeterol, 30 mo		
	Baseline	6 mo	30 mo	Baseline	6 mo	30 mo	Baseline	6 mo	30 mo	Baseline	6 mo	30 mo
Total cell count, $\times 10^6$ cells/mL	168 (77-235)	62 (41-212)	107 (18-268)	117 (53-380)	101 (80-320)	95 (57-164)	175 (101-316)	95 (53-178)	58 (23-74)	136 (78-247)	114 (60-201)	55 (17-160)
Neutrophils, %	72 (54-80)	74 (54-81)	70 (50-85)	73 (63-82)	67 (56-79)	75 (61-79)	66 (50-77)	68 (47-78)	71 (45-79)	72 (61-81)	74 (64-81)	75 (65-81)
Eosinophils, %	0.9 (0.3-2.2)	0.8 (0.2-1.3)	1.0 (0.2-1.8)	1.3 (0.5-2.6)	1.0 (0.5-1.6)	1.0 (0.5-1.9)	1.2 (0.3-2.2)	0.8 (0.2-1.9)	0.8 (0.5-1.8)	1.3 (0.2-2.3)	0.8 (0.4-1.3)	0.8 (0.3-2.0)
Macrophages, %	22 (16-36)	23 (16-39)	22 (11-31)	22 (13-27)	20 (14-34)	20 (15-28)	29 (19-37)	25 (17-37)	19 (14-38)	23 (17-32)	19 (14-31)	19 (16-29)
Lymphocytes, %	1.8 (1.3-3.0)	1.7 (1.0-3.2)	1.8 (1.2-3.7)	1.8 (1.5-2.2)	1.5 (1.2-2.3)	2.0 (1.2-3.3)	2.2 (1.2-3.1)	2.0 (1.2-2.9)	1.9 (1.1-2.3)	1.3 (0.8-2.4)	2.0 (0.7-2.8)	1.7 (1.2-2.5)

* Data are expressed as medians (25th - 75th percentiles)

fluticasone alone on these outcomes, with a change of 0.1 point/y (CI, 0.04 to 0.2 points/y; $P = 0.003$) in total score, 0.1 point/y (CI, 0.03 to 0.3 points/y; $P = 0.013$) in symptom score, and 0.1 point/y (CI, 0.03 to 0.2 points/y; $P = 0.012$) in functional score.

We analyzed the data by using a model that also included individual variances of the slopes and obtained similar results.

Figure 4. Correlation between pathological and clinical outcomes



Upper panel. Correlation of changes (30 months minus baseline) in postbronchodilator forced expiratory volume in one second (FEV_1 , % predicted) with changes in log-transformed $CD4^+$ cell numbers ($/10^{-7} \text{ m}^2$) (4A) and changes in log-transformed mast cell numbers ($/10^{-7} \text{ m}^2$) (4B) in the lamina propria of bronchial biopsies in COPD patients treated with fluticasone propionate 30 months or placebo. Lower panel. Correlation of changes (30 months minus baseline) in log-transformed provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) with changes in log-transformed $CD4^+$ cell numbers ($/10^{-7} \text{ m}^2$) (4C) and changes in log-transformed mast cell numbers ($/10^{-7} \text{ m}^2$) (4D) in the lamina propria of bronchial biopsies in COPD patients treated with fluticasone propionate 30 months or placebo.

Table 4. Bronchial epithelial features at baseline and after 6 and 30 month*

	Placebo, 30 mo			Fluticasone, 6 mo, Then Placebo, 24 mo			Fluticasone, 30 mo			Fluticasone Plus Salmeterol, 30 mo		
	baseline	6 mo	30 mo	baseline	6 mo	30 mo	baseline	6 mo	30 mo	baseline	6 mo	30 mo
Intact epithelium, %	23 (18-35)	22 (10-30)	12 (3-20)	30 (18-42)	21 (10-30)	15 (4-27)	20 (14-33)	20 (14-28)	16 (10-31)	29 (16-47)	29 (24-38)	25 (20-50)
Squamous-cell metaplasia, % of epithelium	0 (0-30)	0 (0-0)	0 (0-0)	0 (0-8.4)	0 (0-0)	0 (0-8.4)	1.1 (0-21)	0 (0-0)	0 (0-0)	0 (0-24)	0 (0-0)	0 (0-0)
Squamous-cell metaplasia, % of patients	24	20	24	26	26	26	25	27	25	25	26	25
PAS/AB-positive area, %	15 (5.9-20)	17 (8.2-26)	9.9 (4.3-27)	8.4 (3.3-20)	14 (6.1-20)	5.0 (1.0-12)	9.2 (3.9-15)	20 (7.9-32)	9.1 (4.6-23)	10 (4.7-16)	17 (8.0-24)	13 (4.9-23)
Ki-67* cells, per mm of basement membrane	15 (3.6-23)	6 (0.5-28)	3.4 (1.6-8.6)	9.9 (3.7-34)	5.4 (1.2-30)	33 (9.3-67)	12 (0.2-39)	4.1 (0.4-12)	5.4 (1.3-13)	9.2 (5.6-33)	7.3 (1.5-25)	11 (6.2-36)

* PAS/AB = periodic acid-Schiff/Alcian blue.

Data are expressed as medians (25th - 75th percentiles).

Smoking and treatment effects

During the study, 3 patients started smoking and 13 patients stopped smoking (balanced among groups). All above results remained statistically significant when adjusted for smoking status throughout the study, except for the reduction in sputum lymphocyte numbers by long-term fluticasone therapy.

Relation of treatment effects with pathology and lung function

Analyses of patients that received either fluticasone or placebo for 30 month showed that decreases in CD4⁺ cells were associated with improvements in predicted postbronchodilator FEV₁ (Rs, -0.35; P = 0.037) (Figure 4). Improvements in methacholine PC₂₀ were associated with reductions in CD3⁺ cells (Rs, -0.36; P = 0.041), CD4⁺ cells (Rs, -0.38; P = 0.034), and mast cells (Rs, -0.46; P = 0.007), and increases in Percentage intact epithelium (Rs, 0.40; p = 0.024) (Figure 4).

Discussion

Our study shows that 2.5-year maintenance therapy with ICS in COPD reduces bronchial T lymphocyte and mast cell numbers and increases eosinophils and the integrity of bronchial epithelium, with an accompanying reduction in sputum cell counts. These effects are associated with a reduced rate of FEV₁ decline and improvements in airway hyperresponsiveness, dyspnea, and health status. Stopping ICS therapy at 6 months leads to relapse of bronchial inflammation and hyperresponsiveness, dyspnea, and poorer health status, with acceleration of FEV₁ decline. Combination therapy with ICS and a long-acting β_2 -agonist does not provide further anti-inflammatory effects compared with fluticasone alone but improves the level of FEV₁ without further influencing FEV₁ decline. Our findings indicate that a subphenotype of patients with COPD who are steroid-naïve and have moderate airway obstruction and airway hyperresponsiveness are sensitive to long-term ICS therapy. These prolonged effects on inflammation and lung function do not imply causality but suggest that disease modification can be achieved in particular phenotypes of patients with COPD.

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We observed differential effects of ICS on inflammatory cell counts. Although smoking may reduce corticosteroid responsiveness [31], our data show that at least part of the inflammation in COPD remains sensitive to this treatment. The contribution of CD8⁺ cells to inflammation and the relevant antigen-specific triggers in COPD are still unknown. CD4⁺ cells may contribute to activation and memory formation of CD8⁺ cells, as well as provide help for B cells [32]. Mast cells and their secreted enzymes can drive various processes relevant to inflammation and remodeling [33]. Although in vitro studies suggest that corticosteroids are less effective in inhibiting activation of mast cells than activation of T-cells [34], our data indicate corticosteroids can have selective anti-inflammatory effects in COPD.

The observed increase in intact epithelium by ICS has also been found in persons with asthma [35]. Corticosteroid-induced changes in epithelial integrity and inflammation correlated with improvements in methacholine PC₂₀, which supports the notion that airway hyperresponsiveness in COPD can be a marker of disease activity [36;37].

The clinical novelty of our findings is that anti-inflammatory effects observed with long-term ICS treatment associate with reduced FEV₁ decline in COPD. Previous short-term studies that investigated patients with COPD and similar degrees of airway obstruction [20;21;38] have shown anti-inflammatory effects of ICS in COPD. We show that these beneficial

effects are maintained during long-term treatment up to 30 months. The detrimental effects of discontinuing ICS therapy on bronchial inflammation are also novel. Previous short-term studies of the combination of a LABA and ICS demonstrated anti-inflammatory effects versus placebo [39] or additional reductions of bronchial CD8⁺ cells and macrophages versus ICS alone [22]. Our data suggest that this is not a long-lasting additional effect; we observed a slight increase in CD3⁺ and plasma cells. The attenuated FEV₁ decline in our patients with COPD contrasts with large COPD trials from the 1990s [7-9]. The more recent TORCH study [15] did show reductions of FEV₁ decline in patients with COPD who received therapy ICSs, LABAs, or both. Our results suggest that the improvement in the level of FEV₁ in the combination group might be due to a residual bronchodilator effect of salmeterol and not further disease modification. Discrepancies between the previous trials and our study may be due to differences in study samples, which may provide a clinical message. Our study comprised a common subset of patients with COPD. First, by choosing steroid-naïve patients, we aimed to exclude patients with unknown previous benefits from ICS at baseline and avoid the problem of selective dropouts in the placebo group. Second, our patients had predominantly moderate degrees of airway obstruction and most demonstrated airway hyperresponsiveness or modest reversibility of FEV₁. Recent studies [10;40] show that these characteristics, previously attributed to asthma alone, can also be components of COPD. This COPD phenotype may be particularly sensitive to ICS, similar to the documented beneficial effects of smoking cessation [37]. Of note, the decrease in postbronchodilator FEV₁ in the placebo group was quite similar to that observed in previous studies [8;10;15]. We were particularly careful to exclude patients with a previous or concurrent diagnosis of asthma by carefully taking histories, checking family practice medical records, and obtaining clinical judgments from chest physicians. Furthermore, most patients had low numbers of eosinophils in sputum and biopsies (similar to those reported by Bourbeau and colleagues [22]), had smoked for many years, and had a mean reversibility of FEV₁ to salbutamol of only 7% of predicted value, and most (83%) were nonreversible according to European Respiratory Society criteria - yet all adhered to the GOLD criteria. This is consistent with the patient characteristics of short-term COPD studies that show benefits with ICS therapy [22;39]. Airway hyperresponsiveness was similar to that in the Lung Health COPD study [10], which measured long-term changes in airway hyperresponsiveness. Finally, our post hoc analysis showed that actual smoking throughout the study was unlikely to be a major

confounder. Taken together, our findings suggest that ICS therapy, when given for the first time and for longer duration to steroid-naïve patients with relatively moderate disease, has the potential to change the clinical course of COPD.

Our study has limitations. First, only 77 of 101 analyzed patients had biopsies at 30 months because patients dropped out or were unwilling to have another bronchoscopy. This might have resulted in selection bias; however, lost-to-biopsy rates were similar among treatment groups. Second, our study was not powered to examine clinical outcomes. Nevertheless, the primary and secondary outcome parameters were all pre-specified. According to international standards on clinical investigations [41], the secondary outcomes point toward a clinically relevant treatment benefit, given our positive findings in the primary outcome. In addition, the positive findings on FEV₁ decline are consistent with the symptomatic benefit we observed [42]. Third, because this was an efficacy trial, we used data from adherent patients. As expected, the placebo group had more nonadherent patients, which may have led to underestimate the treatment effect. Fourth, the pathologic changes in COPD are not uniformly distributed among central and peripheral airways [43;44]. We inevitably focused on the central airways. Fifth, despite its beneficial effects, long-term ICS treatment has potentially meaningful adverse effects, such as increased frequency of pneumonia [14]. Our sample size was too small to draw conclusions on this.

Our study should lead to subsequent analyses of the benefits of inhaled steroids in COPD. Histological outcomes need to include inflammatory and epithelial cell activity and aspects of airway wall remodeling and fibrosis. Studies are also needed to determine the best inflammatory and clinical predictors of steroid efficacy in COPD. Finally, our results indicate a need to study the cost benefit of changing disease progression by using maintenance ICS therapy.

In conclusion, long-term maintenance therapy with ICS can reduce inflammation in bronchial biopsies and sputum in COPD. This is mirrored by attenuated lung function decline, airway hyperresponsiveness, dyspnea, and improved quality of life. Adding a LABA provided supplementary benefit for lung function but did not further alter the course of FEV₁ decline. Clinicians who are treating patients recognize that COPD is a heterogeneous disease that includes various phenotypes [45]. Our observations indicate that progressive decline in lung function can be attenuated in steroid-naïve patients with moderate COPD, a long history of smoking, and airway hyperresponsiveness. The observed treatment response by this particular subphenotype of COPD

underscores the potential of tailored therapy in COPD to achieve clinical benefit.

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Langdurige behandeling met inhalatiesteroiden heeft gunstig effect bij matig ernstige COPD*

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Samenvatting

Doel: De effecten bepalen van een langdurige behandeling met inhalatiesteroïden, met en zonder langwerkende β_2 -agonisten, op luchtwegontsteking en longfunctie bij COPD.

Opzet: Gerandomiseerd, placebogecontroleerd onderzoek in 2 Nederlandse centra (<http://clinicaltrials.gov/ct2/show/NCT00158847>).

Methode: 114 steroïdnaïeve patiënten met matig tot ernstig COPD (rokers en ex-rokers) werden dubbelblind behandeld met: fluticasonpropionaat 500 μ g 2 dd gedurende 6 (n = 31) of 30 maanden (n = 26), of met fluticasonpropionaat 500 μ g 2 dd en salmeterol 50 μ g 2 dd gedurende 30 maanden (n = 28), of met placebo 2 dd (n = 29). Celtellingen in bronchiale biopsen en geïnduceerd sputum dienden als primair resultaat. Luchtweghyperreactiviteit werd gemeten voor randomisatie, na 6 en 30 maanden; klinische parameters werden elke 3 maanden bepaald.

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Resultaten: 101 Patiënten waren meer dan 70% therapietrouw. Na 6 maanden fluticasonegebruik was het aantal lymfocyten (CD3⁺, CD4⁺ en CD8⁺) en mestcellen in de luchtwegwand verminderd (allen $p < 0,005$) en de hyperreactiviteit verbeterd ($p < 0,05$) ten opzichte van placebo. Deze effecten bleven behouden na 30 maanden. Langdurige behandeling met fluticason gedurende 30 maanden verminderde het aantal mestcellen en verhoogde het percentage intact epitheel in de bronchusbiopsen. In het sputum verminderde het aantal neutrofielen, macrofagen en lymfocyten. Deze veranderingen gingen gepaard met een verminderde achteruitgang van de longfunctie en een verbetering van de kortademigheid en de kwaliteit van leven. Na staken van fluticasonegebruik na 6 maanden verhoogde het aantal CD3⁺-cellen, mestcellen en plasmacellen significant en verslechterde het klinische resultaat. Toevoeging van salmeterol aan de behandeling verbeterde het niveau van het geforceerde expiratoire 1-secondevolume (FEV₁).

Conclusie: Behandeling met inhalatiecorticosteroïden kan de luchtwegontsteking en de versnelde afname van de longfunctie verminderen bij steroïdnaïeve patiënten met matig tot ernstig COPD. Het toevoegen van langwerkende β_2 -agonisten versterkte deze effecten niet.

Introductie

Kortdurende behandeling met inhalatiecorticosteroïden (ICS) heeft gunstige effecten bij chronische obstructieve longziekte (COPD). De effecten van langdurige ICS-behandeling zijn echter nog onduidelijk.

COPD wordt gekenmerkt door een progressieve afname van longfunctie gecombineerd met luchtwegklachten en verslechtering van de gezondheidsstatus [1]. De aandoening wordt in verband gebracht met ontsteking in de luchtwegwand [2-4].

De huidige richtlijnen adviseren om patiënten met ernstige COPD en frequent optredende exacerbaties te behandelen met ICS in combinatie met langwerkende β_2 -agonisten (LABA's) [1]. ICS-behandeling leidt tot verbetering van symptomen, vermindering van exacerbatiefrequentie en tot initiële verbetering van longfunctie [5-8]. Bij staken van ICS-behandeling verslechtert het klinisch beeld [9]. Indien de behandeling bestaat uit een combinatie van ICS en een LABA verbetert het klinisch beeld meer dan bij behandeling met ICS alleen [10;11].

Een recent onderzoek suggereert dat langdurige behandeling met ICS of LABA de progressieve afname van het geforceerde expiratoire 1-secondevolume (FEV_1) kan remmen bij COPD [12]. Dit is in tegenstelling tot eerdere onderzoeken, waaruit bleek dat langdurige behandeling met ICS of LABA bij COPD geen effect had op de afname van FEV_1 [13-16].

De klinische effecten van ICS- en LABA-behandeling bij COPD kunnen gedeeltelijk berusten op anti-inflammatoire werking. Behandeling met ICS gedurende 2-3 maanden verminderde het aantal mestcellen, maar niet het aantal $CD8^+$ -cellen, neutrofielen of macrofagen in bronchusbipten [17;18]. Combinatiebehandeling met ICS en LABA gedurende 3 maanden gaf meer anti-inflammatoire effecten dan ICS als monotherapie, [19] maar deze effecten werden niet op de lange termijn bestudeerd.

Het doel van dit onderzoek was om de effecten van ICS op zowel pathologische als klinische kenmerken van COPD te onderzoeken tijdens een langdurige behandeling van 30 maanden.

Patiënten en methoden

Setting en deelnemers

Het 'Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease'(GLUCOLD)-project had een dubbelblinde, parallelle, placebogecontroleerde, gerandomiseerde opzet met 4 groepen [20].

Rokers en ex-rokers met > 10 pakjaren en COPD werden ingesloten (leeftijd:

45-75 jaar). Hun longfunctie was matig tot ernstig verstoord [1]. Exclusiecriteria waren: een voorgeschiedenis van astma, of huidige symptomen, diagnose of behandeling daarvan of -voor, en ICS-behandeling in de 6 maanden voorafgaande aan het onderzoek. Standaard werd geadviseerd om te stoppen met roken. Patiënten werden geworven in huisartsenpraktijken. De ethische commissies van beide centra in Leiden en Groningen keurden het onderzoek goed; alle patiënten gaven schriftelijke toestemming.

Randomisatie van interventies

118 Patiënten werden gerandomiseerd in 4 behandelgroepen: (a) fluticasonpropionaat 500 µg 2 dd gedurende 6 maanden, gevolgd door placebo 2 dd gedurende 24 maanden; (b) fluticasonpropionaat 500 µg 2 dd gedurende 30 maanden; (c) fluticasonpropionaat 500 µg 2 dd en salmeterol 50 µg 2 dd gedurende 30 maanden; (d) placebo 2dd gedurende 30 maanden. Actieve medicatie en placebo werden geïnhaleerd via identieke Diskus-poederinhalatoren (GlaxoSmithKline, Zeist, Nederland). Minimisatie (het gelijk verdelen van patiënten met hun prognostische factoren over de verschillende behandelarmen; elke nieuwe patiënt wordt gerandomiseerd op basis van de verdeling van prognostische factoren die op dat moment aanwezig is) vond plaats voor centrum, geslacht, rookstatus, de verhouding FEV₁: inspiratoire vitale capaciteit (IVC) (< 60 of ≥ 60%) en de provocatiedosis methacholine die nodig was om het FEV₁ 20% te laten dalen (PD₂₀-methacholine) (< 2 of ≥ 2 mg/ml).

Onderzochte parameters

De primaire uitkomstmaat was het aantal inflammatoire cellen in bronchusbiopten en in geïnduceerd sputum [20;21]. De details over bronchoscopie, biopsieverwerking en kwantificatie zijn beschreven in een eerder artikel met baselinegegevens [22]. Spirometrie na luchtwegverwijding en hyperreactiviteit (PD₂₀-methacholine) waren secundaire uitkomstmaten [20]. Kortademigheid werd gemeten met een aangepaste 'Medical research council(MRC)-kortademigheidschaal'; gezondheidsstatus met de 'St. George's respiratory questionnaire' (SGRQ) en 'Clinical COPD questionnaire' (CCQ) [23]. In de CCQ is een verandering in score van 0,4 punten ten opzichte van baseline de kleinste verandering die klinisch significant genoemd kan worden [24].

Follow-up

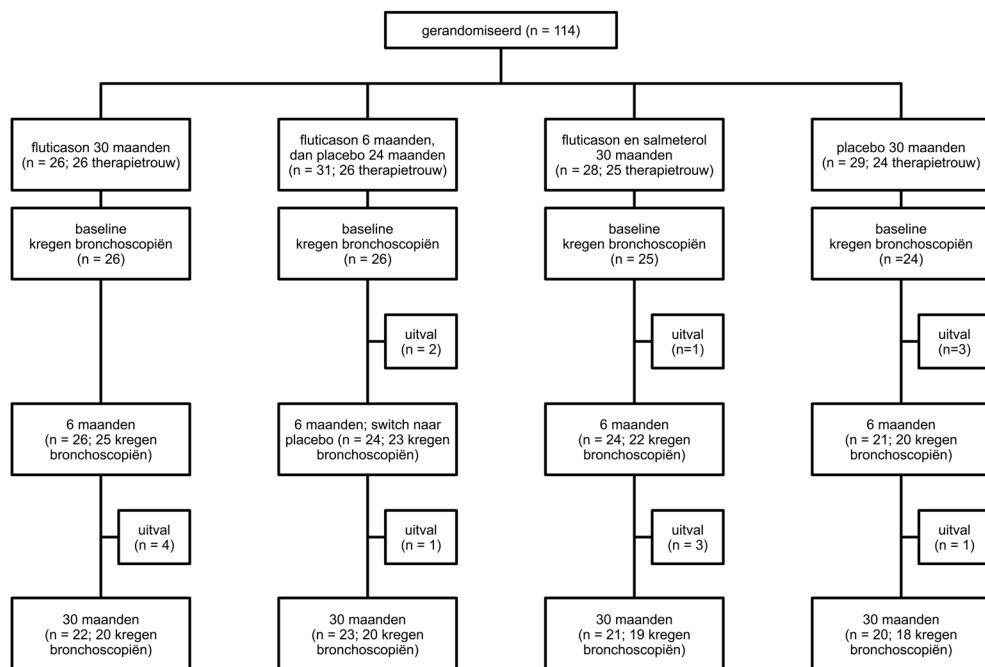
Elke 3 maanden werden symptomen, gezondheidsstatus, rookstatus, therapietrouw (tellen van aantal doses) gemeten en spirometrie verricht. Bronchoscopie, sputuminductie en methacholineprovocatie werden bij de start uitgevoerd, en na 6 en 30 maanden.

Statistische analyse

De steekproefgrootte werd gebaseerd op fluticason-geïnduceerde kortetermijnverandering van de submucosale CD8⁺-celaantallen bij COPD [25]. Bij een aantal van 20 patiënten per behandelgroep is een halvering van CD8⁺-celaantallen in de fluticasongroep in vergelijking tot placebo met een onderscheidingsvermogen ('power') van 80% detecteerbaar [25]. Omdat het een onderzoek naar de werkzaamheid betrof, werd een per-protocolanalyse uitgevoerd bij alle compliante patiënten (> 70% van de voorgeschreven doses gebruikt).

Met lineaire 'mixed effect'-modellen (STATA versie 9.0; StataCorp, Texas,

Figure 1.



Stroomdiagram van een studie naar effecten van langdurige behandeling met inhalatiecorticosteroïden bij matig ernstig COPD. Per behandelgroep is weergegeven het totaal aantal patiënten dat gerandomiseerd werd en dat therapietrouw (>70% van de voorgeschreven dosis ingenomen) was. Voor elke fase van de studie (0, 6 en 30 maanden) zijn de aantallen patiënten vermeld die een bronchoscopie ondergingen.

*Tabel 1. Studie naar effecten van langdurige behandeling met inhalatiecorticosteroiden bij matig ernstig COPD; karakteristieken van 101 therapietrouwe patiënten bij aanvang van de studie**

Karakteristieken	Behandeling, duur				P-waarde †
	Placebo	Fluticasonpropionaat		Fluticasonpropionaat en salmeterol	
	30 maanden (n = 24)	6 maanden, daarna 24 maanden placebo (n = 26)	30 maanden (n = 26)	30 maanden (n = 25)	
klinisch					
man / vrouw; n / n	20 / 4	22 / 4	23 / 3	22 / 3	0,94
leeftijd; jaren	59 (8)	64 (7)	62 (8)	62 (8)	0,31
huidige roker / niet-roker; n/n	17 / 7	14 / 12	16 / 10	17 / 8	0,61
pakjaren roken; mediaan (bereik)	42 (34-54)	41 (29-57)	44 (31-55)	47 (31-56)	0,62
longfunctie					
FEV ₁ ; % voorspeld					
vóór luchtwegverwijding	54,1 (8,3)	56,8 (11,0)	56,6 (9,9)	55,0 (11,0)	0,74
na luchtwegverwijding	61 (8,3)	65 (8,6)	64 (9,1)	61 (9,4)	0,41
verandering in FEV ₁ ; % voorspeld ‡	7,1 (4,5)	7,3 (5,3)	7,1 (4,0)	6,2 (6,3)	0,87
FEV ₁ / IVC na luchtwegverwijding; %	47 (9,0)	51 (8,3)	49 (9,0)	46 (8,4)	0,16
geometrisch gemiddelde PD ₂₀ -metacholine; mg/ml	0,7 (2,0)	0,7 (3,2)	0,4 (2,4)	0,7 (2,7)	0,64
K _{co} ; % voorspeld	65 (19)	79 (29)	77 (22)	74 (27)	0,19
luchtwegklachten en gezondheidsstatus					
MRC-dyspneu-score §	2,7 (0,8)	2,5 (0,6)	2,6 (0,6)	2,9 (1,0)	0,53
SGRQ-score; totaal	33,5 (18,5)	25,7 (15,2)	32,9 (10,9)	28,1 (13,2)	0,27
CCQ-score; totaal ¶	1,77 (1,3)	1,16 (0,6)	1,26 (0,6)	1,43 (0,7)	0,35

120 FEV₁ = geforceerde expiratoire 1-secondevolume; IVC = inspiratoire vitale capaciteit;
PD₂₀-methacholine = de provocatieve concentratie van methacholine die een afname van 20% in FEV₁ veroorzaakt;
KCO = diffusiecapaciteit voor CO; MRC = 'Medical research council'; SGRQ = 'St. George's respiratory questionnaire'; CCQ = 'Clinical COPD questionnaire'.
* Waarden zijn gemiddelden (SD) tenzij anders vermeld.
† Variantieanalyse of kruskal-wallistoets tussen groepen.
‡ Reversibiliteit in FEV₁ na inhalatie van 400 µg salbutamol.
§ Bereik van 1 tot 5 (een hogere score betekent meer dyspneu).
|| Bereik van 0 (best) tot 100 (slechtst).
¶ Bereik van 0 (best) tot 6 (slechtst).

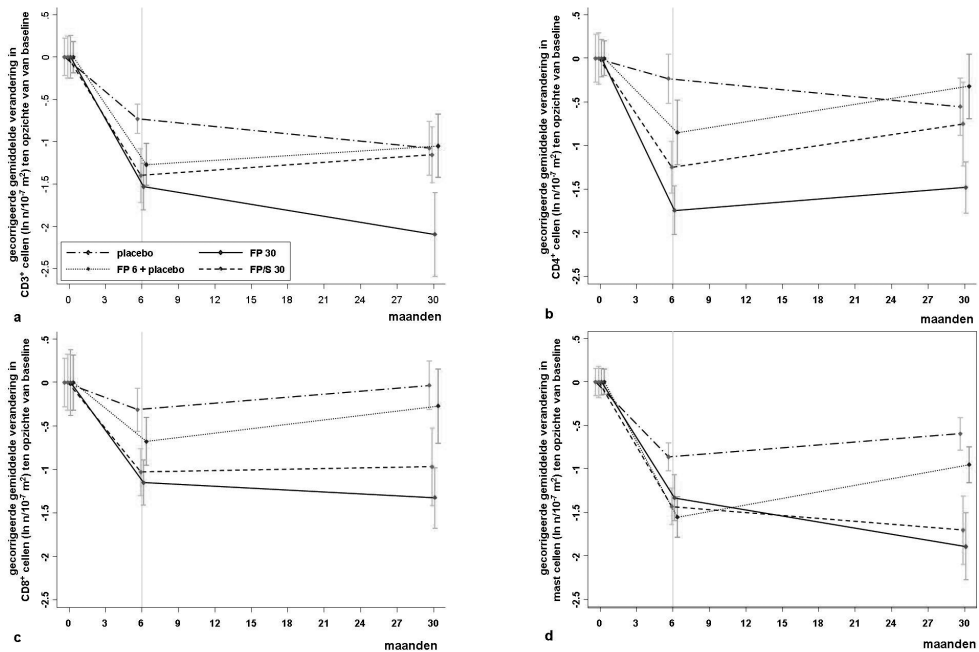
VS) werd het effect van de behandeling, tijd en de interactie van behandeling en tijd geanalyseerd [20]. Een post-hocanalyse onderzocht effecten van de rookstatus. Correlaties tussen statistisch significante behandel-effecten op inflammatoire cellen en longfunctie werden geanalyseerd met de spearman-rangcorrelatiecoëfficiënt. De gegevens worden weergegeven als gemiddelden (SD) of medianen (interkwartielbereiken); een 2-zijdige p-waarde < 0,05 werd als statistisch significant beschouwd.

Resultaten

Van de 114 geïncludeerde patiënten werden 101 therapietrouwe patiënten geanalyseerd (Figuur 1). Van hen hadden 7 ooit een korte kuur met orale corticosteroiden gehad en 5 hadden ooit ICS gebruikt. De

patiëntkarakteristieken bij aanvang van het onderzoek waren vergelijkbaar tussen de 4 behandelgroepen (Tabel 1), evenals het aantal inflammatoire cellen in het sputum en de bronchusbiopten.

Figuur 2.



Uitkomsten van pathologisch onderzoek in een studie naar de effecten van langdurige behandeling met inhalatiecorticosteroiden bij matig ernstig COPD. De grafieken tonen de aangepaste gemiddelde verandering in loggetransformeerde cel aantallen in bronchusbiopten (per 10⁷ m² lamina propria) tijdens behandeling met fluticasonpropionaat 500 µg 2 dd gedurende 30 maanden, fluticasonpropionaat 500 µg 2 dd gedurende 6 maanden, de combinatie van fluticasonpropionaat/salmeterol 500/50 µg 2 dd gedurende 30 maanden en placebo gedurende 30 maanden. 'Error bars' geven het 95%-betrouwbaarheidsinterval weer. Weergegeven zijn de gegevens van (a) bronchiale CD3⁺-cellen, (b) CD4⁺-cellen, (c) CD8⁺-cellen en (d) mestcellen.

ICS-behandeling

6 maanden

Behandeling met fluticason verminderde, in vergelijking tot placebo, het aantal bronchiale CD3⁺-cellen met 55% ($p = 0,004$), CD4⁺-cellen met 78% ($p < 0,001$), CD8⁺-cellen met 57% ($p = 0,010$) en het aantal mestcellen met 38% ($p = 0,039$; Figuur 2). Tegelijkertijd nam bij fluticasonbehandeling de PD₂₀-methacholine toe vergeleken met placebobe-handeling (1,5 verdubbende dosering van methacholine; $p = 0,036$) (Figuur 3B), evenals de score van een onderdeel van de CCQ over het mentale welzijn (toename met 0,2 punten, $p = 0,037$).

30 maanden

Tijdens de behandeling met fluticason van 6 tot 30 maanden bleef de afname van het aantal CD3⁺-, CD4⁺- en CD8⁺-cellen in bronchusbiopten behouden vergeleken met placebo (zie Figuur 2). Het aantal mestcellen nam verder af (56%, $p = 0,001$), het aantal eosinofielen nam toe (125%, $p = 0,046$) evenals het percentage intact epitheel (101%, $p = 0,024$). Daarnaast verminderde in het sputum het aantal neutrofielen (58%, $p = 0,047$), macrofagen (57%, $p = 0,041$) en lymfocyten (52%, $p = 0,035$) na 30 maanden, vergeleken met placebo.

Ten opzichte van de gemiddelde FEV₁-waarde na 6 maanden, daalde de waarde na 30 maanden met 79 ml/jaar in de placebogroep, met 62 ml/jaar in de 6-maanden-fluticasongroep en met 16 ml/jaar in de groep met 30 maanden combinatietherapie. In de 30-maanden-fluticasongroep steeg de gemiddelde FEV₁-waarde met 7,3 ml/jaar. Vergeleken met placebo, verbeterde het gebruik van fluticason de jaarlijkse FEV₁-afname van 6 tot 30 maanden met 86 ml/jaar ($p < 0,001$; Figuur 3a).

De verbetering van PD₂₀-methacholine door fluticasonbehandeling in de eerste 6 maanden, vergeleken met placebo, bleef behouden tijdens de volgende 2 jaar (zie Figuur 3b). Gedurende de laatste 2 jaar van het onderzoek verbeterde fluticasongebruik de 'kortademigheidsscore' ($p = 0,003$; Figuur 3c), de 'SGRQ-activiteitscore' ($p = 0,012$), de totale score van de CCQ ($p = 0,036$) en van de 'CCQ-symptoomscore' ($p = 0,026$) en 'CCQ-functionele score' ($p = 0,027$; Figuur 3d).

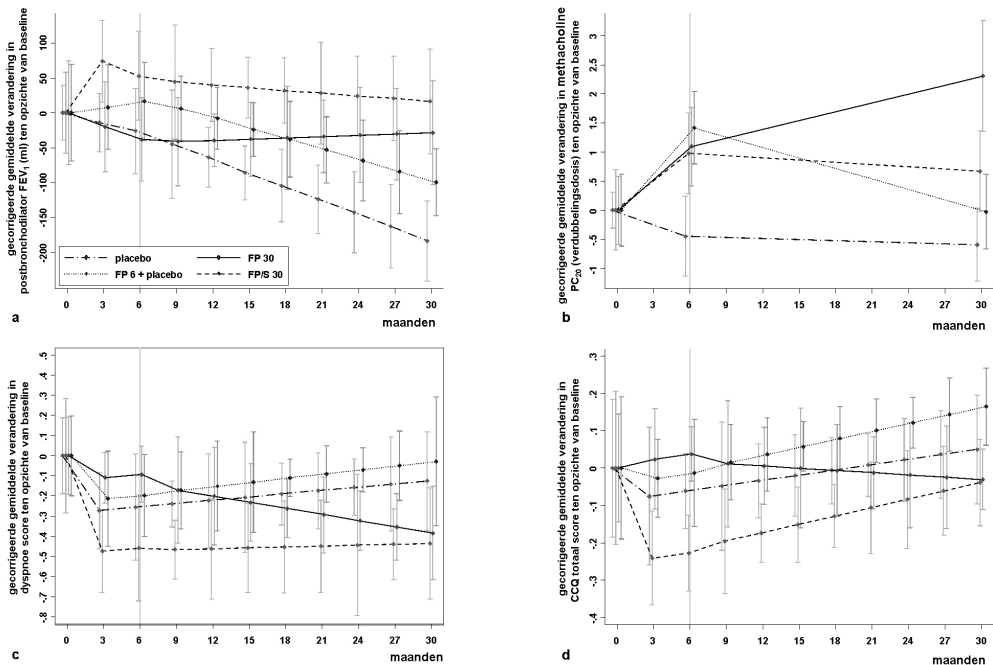
Staken van ICS-behandeling

Staken van fluticasonbehandeling na 6 maanden had geen effect op de aantallen inflammatoire cellen in het sputum en op de epitheelparameters in bronchusbiopten. Wel resulteerde het staken na 6 maanden fluticasonbehandeling in een toename van het aantal CD3⁺-cellen (120%, $p = 0,007$), mestcellen (218%, $p < 0,001$) en plasmacellen (118%, $p = 0,028$) in bronchusbiopten na 30 maanden, vergeleken met de biopten van patiënten die 30 maanden fluticason hadden gebruikt (zie Figuur 2).

De FEV₁-afname van 6 tot 30 maanden was groter na stoppen dan bij continueren van fluticasongebruik (verschil van 70 ml/jaar; $p = 0,001$; Figuur 3a). De PD₂₀-methacholine verslechterde met 2,6 verdubbelingsdoses ($p < 0,001$; Figuur 3b). De kortademigheidsscore daalde met 0,2 punten/jaar ($p = 0,001$; Figuur 3c), evenals de volgende scores: 'SGRQ totale score' (met 1,7 punten/jaar; $p = 0,028$), 'activiteitscore' (met 2,9 punten/jaar; $p = 0,015$), 'CCQ totale score' (met 0,1 punt/jaar; $p = 0,003$) en de 'symptoomscore' (met

0,2 punten/jaar; $p < 0,001$) (gegevens niet getoond).

Figuur 3.



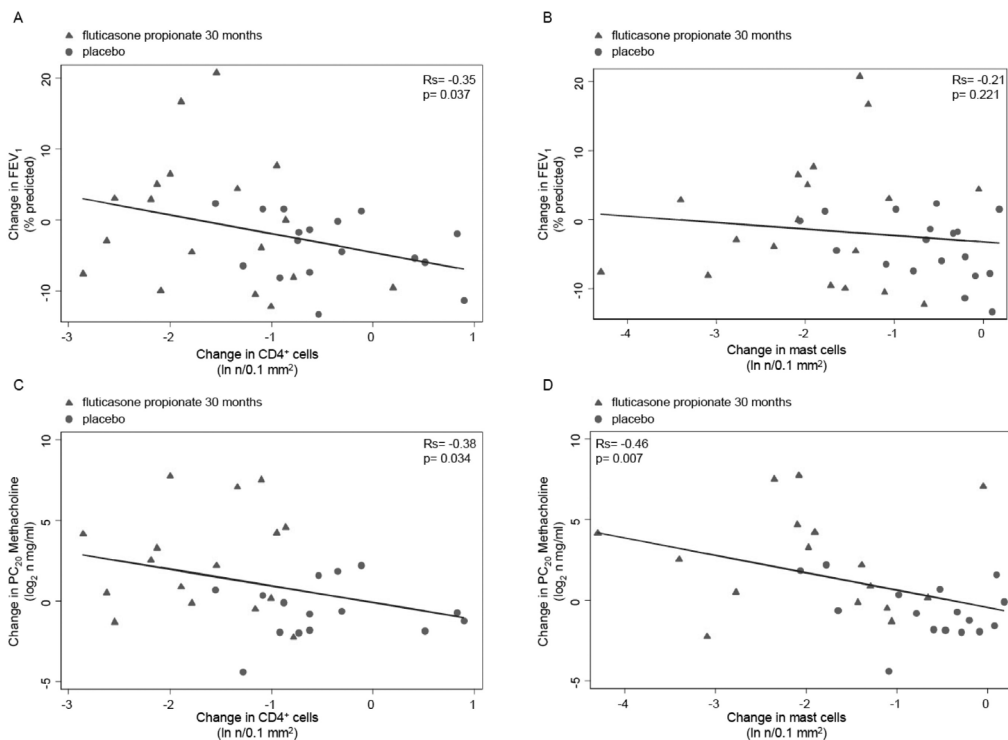
Klinische uitkomsten in een studie naar effecten van langdurige behandeling met inhalatiecorticosteroïden bij matig ernstig COPD. De grafieken tonen de aangepaste gemiddelde verandering met 95%-betrouwbaarheidsintervallen, tijdens de behandeling met fluticasonpropionaat 500 µg 2 dd gedurende 30 maanden, fluticasonpropionaat 500Mg 2 dd gedurende 6 maanden gevolgd door placebo, de combinatie van fluticasonpropionaat/salmeterol 500/50Mg 2 dd gedurende 30 maanden en placebo. Gegevens zijn gepresenteerd als (a) geforceerde expiratoire 1-secondevolume (FEV₁), (b) loggetransformeerde provocatieve concentratie van methacholine die een afname van 20% in FEV₁ veroorzaakt (PD₂₀-metacholine; veranderingen hierin zijn weergegeven als gemiddelde verdubbelingsdosis), (c) 'Medical research council'-dyspneu-score en (d) 'Clinical COPD questionnaire' (CCQ).

Combinatie ICS en langwerkende β_2 -agonisten

Combinatiebehandeling gedurende 6 maanden gaf geen extra anti-inflammatoire effecten vergeleken met fluticasonbehandeling alleen. Na 30 maanden nam het aantal CD3⁺-cellen en plasmacellen toe (126%; $p = 0,006$ respectievelijk 144%; $p = 0,013$; Figuur 2) en het aantal eosinofiele cellen af (55%; $p = 0,047$). Behandeling met salmeterol had geen extra anti-inflammatoir effect op de aantallen cellen in het sputum [20].

Na 6 maanden combinatiebehandeling verbeterde de gemiddelde FEV₁-waarde met 96 ml ($p = 0,018$; Figuur 3a) en de kortademigheidsscores met 0,4 punten ($p = 0,027$; Figuur 3c), meer dan bij fluticasonmonotherapie. Deze initiële verbetering van het FEV₁ werd behouden tijdens de voortgezette combinatiebehandeling, zonder verdere beïnvloeding van de FEV₁-

Figuur 4.



Correlatie tussen verandering in pathologie en klinische uitkomsten bij COPD-patiënten behandeld met fluticason 30 maanden of placebo. Weergegeven zijn correlaties van veranderingen (30 maanden minus baseline) in geforceerde expiratoire 1-secondenvolume (FEV₁, % van voorspeld) na luchtwegverwijdering, met (a) veranderingen van loggetransformeerde CD4⁺-cel aantallen (per 10⁻⁷ m² lamina propria van bronchus biopten; Spearman rangcorrelatiecoëfficiënt (Rs): -0,35; p: 0,037) en (b) met veranderingen in loggetransformeerde mestcel aantallen (per 10⁻⁷ m² lamina propria van bronchusbiopten; Rs: -0,21; p: 0,221). Daaronder zijn weergegeven correlaties van veranderingen (30 maanden minus baseline) in loggetransformeerde provocatieve concentratie van methacholine die een afname van 20% in FEV₁ veroorzaakt (PD₂₀) met (c) veranderingen van loggetransformeerde CD4⁺-cel aantallen (per 10⁻⁷ m² lamina propria van bronchus biopten; Rs: -0,38; p: 0,034) en met (d) veranderingen in loggetransformeerde mestcel aantallen (per 10⁻⁷ m² lamina propria van bronchusbiopten; Rs: -0,46; p: 0,007).

daling, vergeleken met alleen fluticason. De kortademigheidscore nam na 30 maanden toe met 0,1 punt (p = 0,029). Tijdens de eerste 6 maanden combinatiebehandeling verbeterde de 'totale CCQ-score' (p = 0,007), 'symptoomscore' (p = 0,028) en 'functionele score' (p = 0,008) (Figuur 3d). Het minimale klinisch significante verschil van 0,4 werd niet bereikt [24]. Tijdens de daarop volgende 24 maanden verslechterde de 'totale CCQ-score' (p = 0,003), 'symptoomscore' (p = 0,013) en 'functionele score' (p = 0,012) in de groep met combinatiebehandeling.

Roken

Alle bovenstaande resultaten bleven significant na correctie voor rookstatus, behalve het aantal lymfocyten in het sputum na 30 maanden fluticasonbehandeling.

Relatie pathologie en longfunctie

Analyse van patiënten die gedurende 30 maanden fluticason of placebo gebruikten, toonde dat verbetering van de FEV₁-waarden correleerde met afname van CD4⁺-cellen ($p = 0,037$; Figuur 4). Een verbetering in PD₂₀-methacholine correleerde met afname van CD3⁺-cellen ($p = 0,041$), CD4⁺-cellen ($p = 0,034$) en mestcellen ($p = 0,007$) en met toename van het percentage intact epitheel ($p = 0,024$; Figuur 4).

Beschouwing

Ons onderzoek bij COPD toonde aan dat gedurende een ICS-behandeling van 2,5 jaar het aantal bronchiale T lymfocyten en mestcellen verminderde en het aantal eosinofielen en de bronchiale epitheliale integriteit toenam, tegelijk met afname van celaantallen in het sputum. Deze effecten gingen gepaard met een minder snelle FEV₁-afname en met verbetering van luchtweghyperreactiviteit, kortademigheid en gezondheidsstatus. Het stopzetten van de ICS-behandeling na 6 maanden deed deze positieve effecten teniet. De combinatiebehandeling van ICS en LABA bood geen extra anti-inflammatoire effecten vergeleken met fluticasonmonotherapie. Combinatiebehandeling gaf een initiële verbetering van FEV₁ die ook op lange termijn bleef bestaan. Echter, langer doorgaan met behandeling gaf geen verdere beïnvloeding van de daling van FEV₁ ten opzichte van alleen inhalatiecorticosteroïden. Onze bevindingen gaven aan dat een subgroep van COPD-patiënten met een matige tot ernstige luchtwegobstructie, die steroïdnaïef zijn en hyperreactieve luchtwegen hebben, goed reageerde op langdurige ICS-behandeling.

Hoewel roken de reactie op behandeling met corticosteroïden kan verminderen [26], toonden onze gegevens aan dat een deel van de ontsteking bij COPD, ondanks roken, toch gevoelig is voor ICS. De bijdrage van CD8⁺-cellen aan de ontsteking en de relevante antigeen-specifieke triggers bij COPD zijn nog altijd niet bekend. CD4⁺-cellen kunnen bijdragen aan de activering en geheugenvorming van CD8⁺-cellen, evenals B-celactivatie [27]. Mestcellen en hun uitgescheiden enzymen kunnen diverse processen aansturen die relevant zijn voor luchtwegontsteking en remodelering [28].

De klinische nieuws waarde van onze bevindingen is dat anti-inflammatoire effecten bij COPD tijdens 2,5 jaar behandeling met ICS samengaan met een verminderde FEV₁-achteruitgang. Eerder kortdurend onderzoek bij matig tot ernstig COPD toonde reeds anti-inflammatoire effecten van ICS aan [17;18;29]. Ons onderzoek liet zien dat deze gunstige effecten ook op de lange termijn behouden bleven en dat er nadelige effecten op luchtwegontsteking kunnen ontstaan als ICS-behandeling wordt gestopt.

De gevonden vermindering van de FEV₁-afname bij fluticasonbehandeling staat in contrast met eerdere onderzoeken [5-8]. Daarentegen liet het 'Towards a Revolution in COPD Health'(TORCH)-onderzoek [16] ook vermindering van FEV₁-afname zien bij COPD-patiënten die werden behandeld met ICS, LABA's of beide. Onze resultaten suggereren dat de verbetering van het FEV₁-niveau in de combinatiegroep kan worden veroorzaakt door een luchtwegverwijdend effect van salmeterol en niet door een verdere verandering van de onderliggende ontstekings- en remodeleringprocessen. Verschillen tussen eerdere onderzoeken en ons onderzoek kunnen het gevolg zijn van verschillen in selectie van patiëntenpopulatie.

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Door steroïdnaïeve COPD-patiënten te selecteren, sloten we patiënten uit die al gunstige effecten van ICS-behandeling hadden bij aanvang van het onderzoek, en vermeden we dat deze zouden uitvallen in de placebogroep. Onze patiënten hadden overwegend matig ernstige luchtwegobstructie en de meeste patiënten hadden luchtweghyperreactiviteit en geringe reversibiliteit van de obstructie. Hyperreactiviteit past ook bij COPD [8;30] en de reversibiliteit was, met gemiddeld 7%, vergelijkbaar met eerder gepubliceerd interventie-onderzoek bij COPD [6;8;16]. We willen benadrukken dat de diagnose 'astma' bij de patiënten zorgvuldig werd uitgesloten, gebaseerd op het klinische oordeel van longartsen, en raadpleging van huisartsdossiers.

Ons onderzoek heeft enkele beperkingen: (a) 77 van de 101 geanalyseerde patiënten ondergingen na 30 maanden een bronchoscopie; het percentage uitvallers was echter vergelijkbaar tussen de behandelgroepen; (b) de onderzoeksgrootte van de studie was relatief klein om veranderingen in achteruitgang van de longfunctie vast te stellen. Des te opvallender is onze waarneming dat de ICS-geïnduceerde verbeteringen in luchtwegontsteking samenhangen met verbeteringen in longfunctie, hyperreactiviteit en luchtwegklachten; (c) dit was een onderzoek naar werkzaamheid van behandeling, reden waarom we alleen gegevens van therapietrouwe patiënten gebruikten. Zoals verwacht, waren er meer therapieontrouwe patiënten in de placebogroep, waardoor het behandel effect eerder onderschat dan overschat

is; (d) wij onderzochten bipten van de centrale luchtwegen, terwijl de perifere luchtwegen een belangrijke rol spelen bij COPD [31].

Voor de dagelijkse praktijk is het belangrijk om bij deze patiënten met matig ernstig COPD te bepalen wat de beste voorspellers zijn voor een gunstige respons op ICS-behandeling. Daarnaast is het belangrijk om de kosteneffectiviteit te bestuderen van langdurige ICS-behandeling in een pragmatisch onderzoek.

Conclusie

Onze bevindingen suggereren dat behandeling met inhalatiecorticosteroïden (ICS), wanneer deze voor het eerst en langdurig gegeven worden aan steroïdnaïeve COPD-patiënten met een relatief matig ernstig ziektestadium en met aanwezigheid van luchtweghyperreactiviteit, de potentie heeft om het klinische beloop van COPD gunstig te beïnvloeden. Het verminderde de ontstekingsparameters in bronchusbipten en sputum, wat weerspiegeld werd in verminderde achteruitgang van longfunctie, minder hyperreactiviteit en kortademigheid, en verbetering van de kwaliteit van leven. Het toevoegen van een langwerkende β_2 -agonist verbetert de longfunctie, maar verandert de progressie van de aandoening niet. De waargenomen respons op de behandeling bij dit specifieke subfenotype van COPD onderstreept de mogelijkheid voor een behandeling op maat bij COPD en geeft daarmee een nieuw klinisch perspectief.

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