Effects of inhaled corticosteroids on clinical and pathological outcomes in COPD - Insights from the GLUCOLD study

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CHAPTER 5

Relapse in FEV_1-Decline after Steroid Withdrawal in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: We previously observed that 30 months of inhaled corticosteroids (ICS) can attenuate FEV_1-decline in COPD, but it is unclear whether withdrawal induces a relapse. We hypothesized that FEV_1-decline, airway hyperresponsiveness (AHR) and quality of life (QOL) deteriorate after ICS cessation even after prolonged use.

Methods: 114 moderate to severe COPD patients finished randomized treatment with 6-month (F6) or 30-month fluticasone (F30) (500µg, bid), 30-month fluticasone/salmeterol (FS30) (500/50µg, bid) or placebo during GLUCOLD-1 (GL1). The subsequent 5 years [GLUCOLD-2 (GL-2)], patients were prospectively followed annually, treated by their physician. Post-bronchodilator FEV_1, AHR and QOL were initially recorded at baseline, 30 months (GL1) and annually during GL2. Analysis was performed by linear mixed-effects models.

Results: Amongst 101 adherent patients during GL1, 79 patients started and 58 completed GL2. Patients using ICS during GL1, but only using ICS 0-50% of time during GL2 (n=56/79) had significantly accelerated annual FEV_1-decline compared to GL1 (difference GL2-GL1 [95%CI]: FS30 -68ml/year [-112 to -25], P=0.002; F30 -73ml/year [-119 to -26], P=0.002), accompanied by deterioration in AHR and QOL.

Conclusions: ICS discontinuation after 30-month in COPD can worsen lung function decline, AHR and QOL during 5-year follow-up. This suggests that ICS treatment lacks sustained disease modifying effect after treatment cessation.

INTRODUCTION

Patients with stable Chronic Obstructive Pulmonary Disease (COPD) are currently treated with long-acting bronchodilators and in case of frequent exacerbations with inhaled corticosteroids (ICS) [1]. In these patients, ICS use reduces exacerbations, the rate of decline in quality of life (QOL) and the risk of death and hospitalization [2, 3]. However, the effect of ICS on lung function decline remains controversial.

Several studies in COPD presented transient improvements in lung function with ICS, whereas others failed to show benefits on FEV_1, QOL and frequency of exacerbations [4-6]. We have previously reported that 30-month treatment with fluticasone and salmeterol in 114 well-characterized, moderate to severe COPD patients decreased inflammation, attenuated lung function decline and improved QOL [7].

In contrast, long-term effects after ICS withdrawal on lung function and QOL have been little studied. Recent research indicates that discontinuation after 6 weeks of ICS in severe-to-very-severe COPD patients leads to a greater decrease in FEV_1 without effect on the number of exacerbations during a 1-year follow-up compared to the ICS continuation group [8]. Other ICS withdrawal studies found a deterioration in lung function, increased frequency of exacerbations and a lower QOL during 6-12 month follow-up compared to the non-ICS group [9, 10]. Thus, there is a clinical need for careful monitoring disease outcomes after withdrawal of long-term ICS treatment in COPD [11].

We hypothesized that lung function decline, airway hyperresponsiveness (AHR) and health-related QOL deteriorates after withdrawal of ICS in COPD patients who had previously been randomized to 30-month ICS treatment, but had no or reduced ICS treatment during 5 subsequent years of prospective follow-up.

MATERIALS AND METHODS

Patients and design

For the first interventional part of the GLUCOLD [Groningen Leiden Universities

Corticosteroids in Obstructive Lung Disease] study (GL1), a double-blind, placebo-controlled randomized trial, 114 stable, moderate to severe, steroid-naive COPD patients were included [7]. Participants were randomized to receive one of the following twice daily treatments as dry-powder inhaler: 6-month (F6) or 30-month fluticasone propionate (F30; 500µg), 30-month fluticasone with salmeterol (FS30; 500/50µg; single Diskus), or 30-month placebo.

During the present observational, prospective GLUCOLD follow-up study (GL2), participants visited the outpatient clinic annually for 5 consecutive years. At the start of GL2, the participants' physicians were recommended to treat the patients according to the guidelines [12]. This implies that some patients stopped using ICS, whereas others intermittently or continuously used ICS during GL2.

After completion of GL2, the patients' pharmacy presented an overview of delivered medications during the past 5 years of inhaled/oral steroids and antibiotics. Treatment adherence to the prescribed medication during GL2 was not checked.

Post-bronchodilator spirometry and measures of QOL were recorded at baseline and after 30 months (GL1) and subsequently yearly during follow-up (GL2) [7]. AHR to methacholine (PC_{20}) was measured at baseline, after 30 months, 2 and 5 years follow-up. The ethics committees of Leiden University Medical Center and University Medical Center Groningen approved the original and follow-up study. All patients provided new written informed consent for GL2.

Outcomes

The primary outcome was the difference in the annual decline in post-bronchodilator FEV_1 during 5-year of follow-up (GL2) compared to the first 30 months (GL1). Secondary outcomes were differences between GL2 and GL1 in AHR and QOL, measured by the MRC dyspnea score (Medical Research Council), St. George's Respiratory Questionnaire (SGRQ) and Clinical COPD Questionnaire (CCQ) [13-14].

Statistical Analysis

We used only data of adherent patients in GL1 (using ≥70% of the prescribed dose) [7]. Data of participants who did not complete GL2 were also used for analysis and analyzed with SPSS 22.0 software (SPSS Inc. Chicago, IL). The analysis was stratified for original treatment group

and ICS use during GL2. We used linear mixed-effect models with a random intercept for each subject using all FEV_1 measurements during the entire study as outcome variable and an unstructured covariance matrix. To assess the difference in FEV_1-decline between GL1 and GL2 we included two time variables in the models; time1: time since start of GL1 (range 0-7.5 years); time2: time since start of GL2 (range 0-5 years, during GL1 this value is zero). ICS use during GL2, based on delivered prescriptions by the pharmacies, was divided in the following groups: all (compliant) patients; patients without ICS use; patients with 0-50% of the time ICS use (which included the group without ICS use) and patients with 50-100% of the time ICS use. The daily dose of ICS (in µg, in beclomethasone dipropionate (BDP) equivalents) during 5 years was calculated as daily sum of the different doses of ICS (in µg/day) divided by the total time that ICS were used (days). For selected analyses, we combined the original FS30 and F30 groups to increase power. Given the limited sample size of patients completing the 7.5 years of prospective follow-up, possible confounders (smoking, age, sex and center) were not included in the model. A previous post-hoc analysis showed that smoking was unlikely to be a major confounder [7]. Baseline patient characteristics and daily dose of ICS dose were analyzed by Kruskal-Wallis tests, analysis of variance or X^2 tests. Data are presented as change in estimates between GL2 and GL1 with 95% confidence interval (CI), means with standard deviations or medians with interquartile range. Statistical significance was inferred at $P \leq 0.05$ (two-sided).

RESULTS

At the start of the GLUCOLD study (GL1), 114 patients had been randomized to receive one of the above mentioned randomized 30-month treatments; 101 participants were adherent during GL1 [7]. Eighty-six patients completed GL1, 79 started the GLUCOLD follow-up study (GL2) and 58 patients completed GL2 (Figure 1). Patient characteristics at baseline and at start of GL2 (Table 1) were similar among the original treatment groups, except for a significantly higher post-bronchodilator FEV_1 after 30-month treatment among the FS30 and F30 groups, compared to the F6 and placebo groups [7]. Most patients (56/79 patients) did not use any or used 0-50% of the time ICS during GL2. The mean daily ICS dose during 5 years was 960µg (SD 496µg, in BDP equivalents, Table 2), which was not significantly different between the original treatment groups.

	Baseline GL1				Start of GL2			
	F6 (n=26)	F30 (n=26)	FS30 (n=25)	placebo (n=24)	F6 (n=23)	F30 (n=22)	FS30 (n=21)	placebo (n=20)
Gender (M/F) (n)	22/4	23/3	22/3	20/4	20/3	219/3	20/1	18/2
Age (yr)	64.1 (7.4)	62.3 (7.7)	62.1 (7.7)	59.8 (8.2)	65.8 (7.7)	63.1 (7.3)	64.6 (7.1)	63.5 (7.4)
Smoking (y/n) (n)	14/12	16/10	17/8	17/7	10/13	11/11	12/9	11/9
Packyears (yr)	41 (29-57)	44 (31-55)	47 (31-56)	42 (34-54)	42 (28-54)	44 (32-56)	52 (35-57)	46 (37-58)
Post -bronchodilator FEV_1 (%pred)	64.6 (8.6)	63.7 (9.1)	61.2 (9.4)	61.2 (8.3)	63.7 (12.5)	65.0 (11.1)	61.9 (12.1)	57.3 (8.7)
Post-bronchodilator FEV_1 (L)	2.01 (0.47)	2.04 (0.42)	2.01 (0.40)	2.00 (0.55)	1.96 (0.60)	2.06 (0.51)	2.02 (0.51)	1.85 (0.56)
Post-bronchodilator FEV_1/FVC (%)	50.8 (8	48.9 (9.0)	45.6 (8.4)	46.7 (9.0)	50.0 (9.8)	49.1 (9.9)	45.5 (9.7)	42.1 (9.9)
Geometric mean PC_{20} (mg/ml)	0.71 (3.2)	0.41 (2.4)	0.72 (2.7)	0.66 (2.0)	0.94 (2.9)	2.29 (2.9)	1.33 (3.0)	0.36 (2.4)
MRC dyspnea score	2.46 (0.65)	2.62 (0.57)	2.88 (0.97)	2.71 (0.81)	2.61 (1.12)	2.45 (0.67)	2.43 (1.03)	2.60 (1.05)
CCQ total score	1.10 (0.56)	1.26 (0.58)	1.53 (0.76)	1.62 (1.24)	1.37 (0.82)	1.29 (0.57)	1.60 (1.02)	1.49 (1.09)
SGRQ total score	25.7 (15.2)	32.9 (10.9)	28.1 (13.2)	33.4 (18.5)	24.8 (16.9)	28.2 (14.5)	25.7 (13.3)	31.3 (20.0)

Table 1: Patient characteristics at baseline of randomized therapy (GL1) and at the start of 5 years post-treatment follow-up (GL2) for the original GL1 treatment groups. Data are presented as mean and standard deviation, median with interquartile range (for packyears) or numbers. PC_{20} is expressed as mean doubling doses. F6: 6 months treatment with fluticasone and 24 months with placebo; F30: 30 months treatment with fluticasone; FS30: 30 months treatment with fluticasone and salmeterol; PC_{20}: provocative concentration of methacholine that causes a 20% decrease in FEV_1; MRC: Medical Research Council; SGRQ: St. George's Respiratory Questionnaire; CCQ: Clinical COPD Questionnaire.

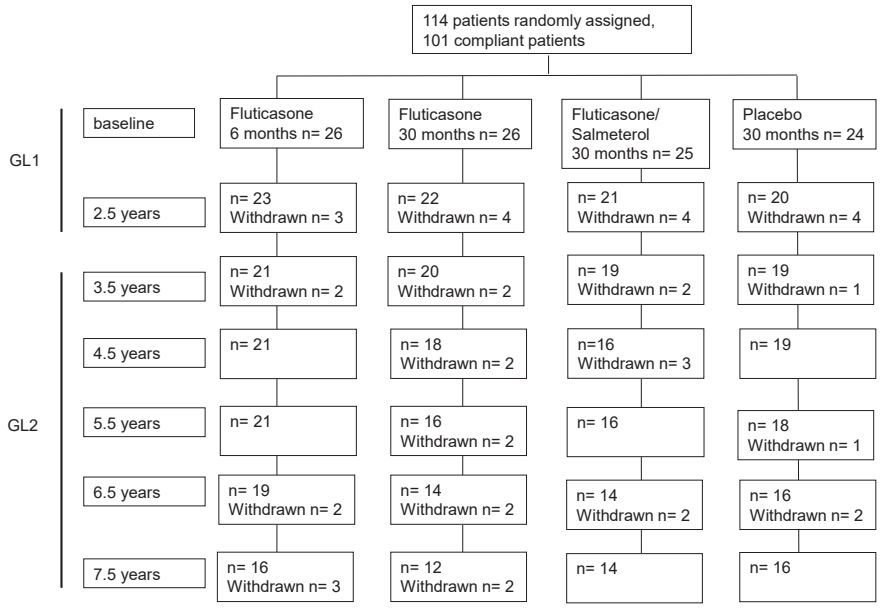

Figure 1: Study flow diagram. Number of randomly assigned patients who were adherent to the original therapy (used ≥70% of prescribed dose during GLUCOLD study (GL1)). After 2.5 years, the GLUCOLD follow-up study (GL2) started. The number of patients who remained in GL2 and those withdrawn are presented.

Lung function decline

Annual FEV_1-decline was significantly faster during GL2 than GL1 in patients who used ICS 0-50% of the time during GL2 in the original FS30 group (difference in FEV_1-decline between GL2 and GL1 (95% CI)) (-68 ml/year [-112 to -25 ml/year]; P=0.002) and F30 group (-73 ml/year [-119 to -26 ml/year]; P=0.002) (Table 3 and Figure 2). When analyzing patients without ICS use during GL2, FEV_1-decline during GL2 compared to GL1 was even more pronounced (original FS30 group: -106 ml/year [-171 to -41 ml/year]; P=0.002; F30 group: -84 ml/year [-149 to -18 ml/year]; P=0.01). Patients in the original combined FS30/F30 groups using ICS 50-100% of the time during GL2 had a decline in FEV_1 of -59 ml/year ([-106 to -11 ml/year]; P=0.02) in GL2 compared to GL1.

Table 2: Number of compliant patients at the start of the GLUCOLD follow-up study (GL2) using ICS and daily dose of ICS (in µg) during 5 years in those patients who used ICS during GL2.
The daily dose of ICS (in µg, in BDP equivalents) during 5 years was calculated by the sum of the different doses of ICS per day (in µg/day), divided by the total time that ICS were used (in days). Doses were based on data provided by the patients' pharmacy.

Original treatment group	No ICS use	≤50% use of ICS (n)	>50% use of ICS (n)	100% use of ICS (n)	Daily dose ICS (µg)
F6	8	7	6	0	671 (383)
F30	10	5	3	2	1025 (590)
FS30	5	6	5	3	1132 (490)
Placebo	11	4	3	1	1049 (418)
Total	34	22	17	6	960 (496)

Daily dose of ICS is presented as means with standard deviations. F6: 6 months treatment with fluticasone and 24 months with placebo; F30: 30 months treatment with fluticasone; FS30: 30 months treatment with fluticasone and salmeterol.

Airway hyperresponsiveness

Patients of the combined original FS30/F30 groups without ICS use and patients who used ICS 0-50% of time during GL2 showed a deterioration in methacholine PC_{20} in GL2 compared to GL1 (-1.3 doubling dose/year [-2.0 to -0.5], P=0.002; -1.1 doubling dose/year [-1.8 to -0.5], P=0.001, respectively). Patients in the original placebo group who used 50-100% of the time ICS during GL2 had an increase in PC_{20} in GL2 compared to GL1 (1.5 doubling dose/year [0.06 to 2.9]; P=0.04).

Table 3: Annual decline in post-bronchodilator FEV_1 (ml/year) during GL2 compared to GL1. Treatment in GL1 (first column) and use of inhaled corticosteroids (ICS) during GL2 (upper row). * P<0.05

Treatment in GL1	all patients (n=79)	no ICS use (n=34)	0-50% ICS use (n=56)	50-100% ICS use (n=23)
F6	-19 (-49 to 11)	-19 (-71 to 33)	-26 (-63 to 10)	-11 (-71 to 50)
F30	-67* (-103 to -30)	-84* (-149 to -18)	-73* (-119 to -26)	-37 (-122 to 48)
FS30	-65* (-98 to -31)	-106* (-171 to -41)	-68* (-112 to -25)	-72* (-128 to -16)
placebo	10 (-18 to 39)	13 (-28 to 54)	-3 (-36 to 31)	34 (-15 to 83)

Data presented as estimates and 95% CI. F6: 6 months treatment with fluticasone and 24 months with placebo; F30: 30 months treatment with fluticasone; FS30: 30 months treatment with fluticasone and salmeterol.

Health-related quality of life

Complete withdrawal of ICS during GL2 in the original combined FS30/F30 groups was accompanied by worsening of the MRC dyspnea score in GL2 by 0.2 points/year (0.06 to 0.3 points/year, P=0.006), SGRQ total score by 2.5 points/year (0.2 to 4.7 points/year, P=0.03), CCQ total score by 0.1 point/year (0.008 to 0.2 points/year, P=0.03) and CCQ symptom score by 0.2 points/year (0.05 to 0.3 points/year, P=0.008) compared to GL1.

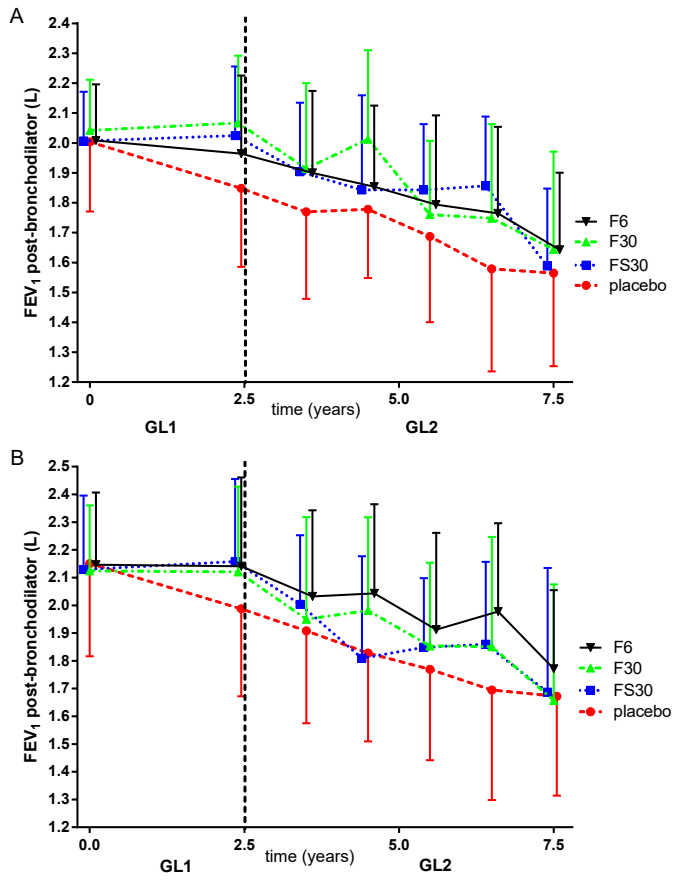

Figure 2: Mean post-bronchodilator FEV_1 (L) and 95% CI during GL1 and GL2 over time for all compliant patients (A, upper part) and those using 0-50% ICS during GL2 (B, lower part) of the four original treatment groups.

F6: 6months treatment with fluticasone and 24 months with placebo; F30: 30 months treatment with fluticasone; FS30: 30 months treatment with fluticasone and salmeterol.

DISCUSSION

This study shows that discontinuation of ICS after long-term use in COPD seems to accelerate lung function decline during subsequent follow-up together with deterioration in AHR and health-related QOL. This indicates that the initial benefits of 30-month ICS treatment on COPD progression are confined to active treatment and are not sustained after long-term cessation of ICS.

This is the first observation that lung function decline significantly accelerates during 5-year follow-up in moderate to severe COPD patients who did not use or intermittently continued ICS after 30-month randomized ICS treatment. Our results on FEV_1 decline are in line with those of previous trials [8-10, 15]. However, different study designs, follow-up time, disease severities, sample sizes and definitions of ICS withdrawal makes it difficult to compare the annual decline in FEV_1 between these studies. Furthermore, QOL measured by MRC, SGRQ and CCQ, deteriorated during long-term follow-up compared to the previous randomized treatment period, although the minimal clinically important difference was not reached [16, 17]. SGRQ total score gradually declines over time after withdrawal of ICS in patients who previously used long-term ICS, which is similar to the decline in SGRQ found in the ISOLDE trial [15]. Our data extends previous observations, showing a deterioration in QOL after discontinuation of ICS compared to salmeterol or placebo during follow-up in COPD patients [9, 10]. Finally, we observed a deterioration in AHR during 5 years after ICS cessation, which thus far had only been described in asthmatics and after short-term treatment in COPD [7, 18, 19]. In contrast to asthma, where AHR is mostly related to the degree of inflammation [20], we previously showed that AHR in this group of COPD patients is associated with both airflow limitation and airway inflammation [7, 21]. Taken together, the present study provides novel data on relapse of FEV_1 decline and AHR after discontinuation of ICS after long-term use in COPD patients.

The strength of our study is represented by its long-term prospective design with repeated monitoring during 5 years of observational follow-up. In addition, the concordance of the currently observed changes in lung function decline, AHR and QOL further contributes to the confidence in our data. Nevertheless, this study had some limitations. First, only half of the patients randomized at baseline completed the entire 7.5-year follow-up, mostly due to the natural course of the disease with associated mortality and comorbidities. This could have led to a loss of statistical power compared to GL1 and a selection bias, even though the number of withdrawn patients during GL2 was similar among the original treatment groups. Second, only few patients used ICS 50-100% of the time during GL2 (n=23). Although only adherent patients during GL1 were used for the follow-up analysis, compliance to inhalation medication was not checked during GL2, thereby reflecting adherence in daily practice [22]. Creating small subgroups of patients using steroids during GL2 made it difficult to detect a difference in annual decline of FEV_1 in the FS30 group between those who used ICS 0-50% and 50-100% of the time during GL2. Third, pneumonia and exacerbation rates were not recorded during GL2, though prolonged use of ICS in COPD may have adverse effects, like the risk of serious pneumonia, especially with high-dose fluticasone [23]. However, retrospectively retrieved rates of antibiotics and prednisolone courses were similar between the groups. Amongst the 26 patients who died during the 7.5-year follow-up only one

patient in the original F6 group (not participating in GL2) died of a pneumonia, yet occurring as complication of a lung carcinoma. Furthermore, overall survival was not statistically different between the original treatment groups. Hence, our data do not allow conclusions on the incidence of pneumonia or exacerbations during or after ICS usage.

How can we interpret our results? Effects of ICS in COPD are affected by the complexity of this heterogeneous disease, classified by clinical, physiologic, pathological and radiologic variables and varies by host susceptibility and/or cigarette smoking [24, 25]. Previously, we described that ICS treatment attenuates lung function decline and decreases inflammation in this group of COPD patients [7]. The present study shows a relapse in lung function decline after discontinuation of ICS. The presently observed rate of decline is higher compared to that in the recent WISDOM study [8]. Moderate to severe COPD patients as in our study are representing a pathophysiological distinct group and thereby potentially more responsive to ICS [4]. The annual rate of decline after ICS discontinuation could therefore be larger compared to severe airflow obstruction [9, 10, 15]. This suggests (at least) temporary disease modification of COPD, especially during active and prolonged periods of ICS use. Future analyses should focus on inflammatory outcomes to determine whether our previously observed anti-inflammatory effects of ICS in COPD are also ablated.

Our results may have consequences for future treatment of COPD patients. Although meta-analyses show limited benefits of ICS in COPD [3], the original GLUCOLD study suggests that maintenance use of ICS can lead to attenuated lung function decline at least in this subset of COPD patients [7]. Notably, the current long-term follow-up study indicates that such benefits are not maintained after prolonged cessation of treatment. Though these data may suggest that ICS treatment in COPD should not be discontinued, this study was not designed to show evidence of any continued benefits of prolonged ICS therapy.

CONCLUSIONS

The present data indicate that discontinuation after 30-month use of ICS in this group of moderate to severe COPD deteriorate lung function decline during 5-years follow-up. This is accompanied by worsening in AHR and a small drop in QOL. These results suggest that, whereas initial long-term ICS use can have a disease modifying effect in particular COPD patients, such benefits disappear when ICS are discontinued.

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