European Journal of General Practice. 2007; 13: 89–95

informa
healthcare

BRIEF RESEARCH REPORTS

Early intervention with inhaled corticosteroids in subjects with rapid decline in lung function and signs of bronchial hyperresponsiveness: Results from the DIMCA programme

JOOST J. DEN OTTER[1], CONSTANT P. VAN SCHAYCK[1], HANS T. M. FOLGERING[2], GUIDO VAN DEN BOOM[1], REINIER P. M. AKKERMANS[1] & CHRIS VAN WEEL[1]

[1]*Department of General Practice and* [2]*Department of Pulmonology, Dekkerswald UMC St. Radboud Nijmegen, Nijmegen, the Netherlands*

Abstract

Background: Asthma is generally accepted as an inflammatory disease that needs steroid treatment. However, when to start with inhaled steroids remains unclear. A study was undertaken to determine when inhaled corticosteroids should be introduced as the first treatment step. *Objective:* To investigate the effectiveness of early introduction of inhaled steroids on decline in lung function in steroid-naïve subjects with a rapid decline in lung function in general practice. *Subjects:* Patients with signs/symptoms suspect of asthma (i.e., persistent and/or recurrent respiratory symptoms) and a decline in forced expiratory volume in 1 s (FEV_1) during 1-year monitoring of 0.080 l or more and reversible obstruction ($\geq$10% predicted) or bronchial hyperresponsiveness ($PC_{20} \leq 8$ mg/ml) were studied. They had been identified in a population screening aiming to detect subjects at risk for chronic obstructive pulmonary disease (COPD) or asthma. *Design:* A placebo-controlled, randomized, double-blind study. *Methods:* 75 subjects out of a random population of 1155 were found eligible, and 45 were willingly to participate. Subjects were randomly treated with placebo or fluticasone propionate 250 μg b.i.d., and FEV_1 and PC_{20} were monitored over a 2-year period. *Outcome variables:* The primary outcome measure was decline in FEV_1; the secondary outcome measure was bronchial hyperresponsiveness (PC_{20}). *Results:* 22 subjects were randomly allocated to the active group with inhaled corticosteroids and 23 to placebo. Change of FEV_1 in the active treated group was +43 ml in post-bronchodilator FEV_1 ($p = 0.341$) and +62 ml/year ($p = 0.237$) in pre-bronchodilator FEV_1 after 1 year, and −22 ml ($p = 0.304$) for post-bronchodilator FEV_1 and −9.4 ml ($p = 0.691$) for pre-bronchodilator FEV_1 after 2 years, compared to placebo. The effect on PC_{20} was almost one dose-step ($p = 0.627$) after 1 year and one dose-step ($p = 0.989$) after 2 years.

Conclusion: In this study, the early introduction of inhaled corticosteroids in newly diagnosed asthmatic subjects with rapid decline in lung function did not prove to be either clinically relevant or statistically significant in reversing the decline in FEV_1. For PC_{20}, no significant changes were detected.

Key words: *Asthma, COPD, early intervention, general practice*

Introduction

Asthma is considered a chronic inflammatory disease that requires anti-inflammatory treatment, even in its earliest phase (1). Inhaled corticosteroids are widely available for treatment, and withholding steroids is assumed to result in irreversible lung function decline (2). However, the efficacy of inhaled corticosteroid treatment to modify this decline in the early phase of the disease has never been studied, and that was the objective of this study. Subjects who had never in their life been diagnosed with asthma or chronic obstructive pulmonary disease (COPD) were recruited for this study from the general population by means of population screening, followed by repeated lung function measurements to assess a rapid decline in lung function and signs of bronchial hyperresponsiveness.

Correspondence: Chris van Weel, Department of General Practice, UMC St. Radboud Nijmegen, 229 HAG, PO Box 9101, 6500 HB Nijmegen, the Netherlands. E-mail: c.vanweel@hag.umcn.nl

ISSN 1381-4788 print/ISSN 1751-1402 online
DOI: 10.1080/13814780701377455

Methods

Fluticasone 250 μg b.i.d. was tested in a 2-year randomized, placebo-controlled study as part of the DIMCA programme (3). This paper reports the second part of this programme. Subjects were invited to participate if a decline in forced expiratory volume in 1 s (FEV_1) of 0.080 l/year had been established during an observation of 12 months as well as the presence of 1) reversibility $\geq 10\%$ predicted and/or 2) moderate bronchial hyperresponsiveness (i.e., $PC_{20} \leq 8$ mg/ml). Salbutamol 400 μg on demand was allowed as the only other concomitant respiratory medication. Exacerbations were treated with a fixed course of prednisolone and antibiotics. Informed consent was obtained from all subjects, and the local ethics committee approved the study.

All lung function measurements were carried out according to European Respiratory Society (4) standards. The primary study endpoint was decline in FEV_1, and the secondary outcome measure was bronchial hyperresponsiveness (PC_{20}). The number of evaluable patients needed was 36 per treatment group (ß = 0.80, $<$ = 0.05). Both an "intent to treat" analysis and an explanatory analysis were done. Repeated measurement analyses were performed using the SAS "PROC MIXED" procedure. All tests were two tailed ($p < 0.05$ was considered statistically significant).

Results

Seventy-five subjects fulfilled the inclusion criteria, of whom 37 showed a $PC_{20} \leq 8$ mg/ml, 13 a reversibility of $\geq 10\%$, while 25 fulfilled both. Forty-five subjects agreed to be included, 32 attended all scheduled follow-up assessments and 13 dropped out (six from the fluticasone group). There were no significant differences between the control group and intervention group, with the exceptions of FVC (3.933 ± 0.777 vs 4.218 ± 1.176), $PC_{20\ \text{geometric mean}}$ (7.46 vs 5.86), pack years (7.7 ± 12.2 vs 9.0 ± 10.2) and symptom score (0.5 ± 0.82 vs 1.44 ± 1.39).

In Figure 1, the course of FEV_1 (post- and pre-bronchodilator) is shown. For the first year, a 43-ml difference in $FEV_{1\ \text{post}}$ ($p = 0.341$) and 62 ml ($p = 0.237$) in $FEV_{1\ \text{pre}}$ was demonstrated in favour of fluticasone. After 2 years, the differences were -22 ml ($p = 0.304$) and -9.4 ml ($p = 0.691$), respectively.

Analysis of PC_{20} showed a non-significant difference over the first year of almost one dose-step in favour of fluticasone ($p = 0.989$). After 2 years, a similar difference was found ($p = 0.989$). The explanatory analysis did not reveal results in another direction (Figure 2).

Discussion

This study investigated the efficacy of early steroid treatment in subjects never in their life diagnosed by

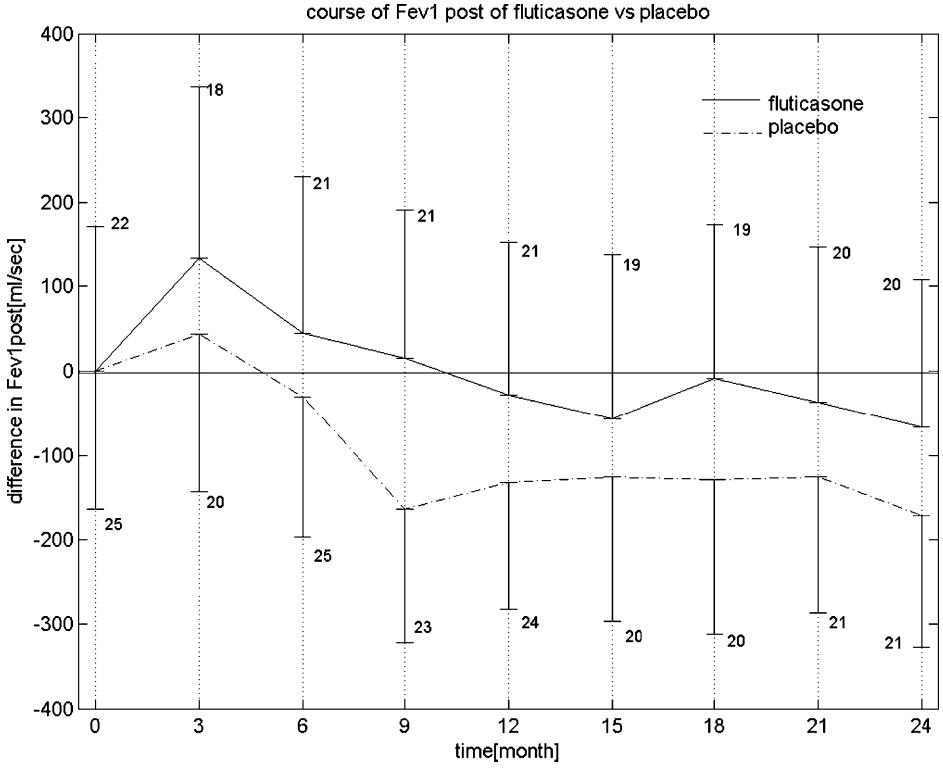

Figure 1. Mean difference in $FEV_{1\ \text{post}}$ from baseline for each point of measurement.

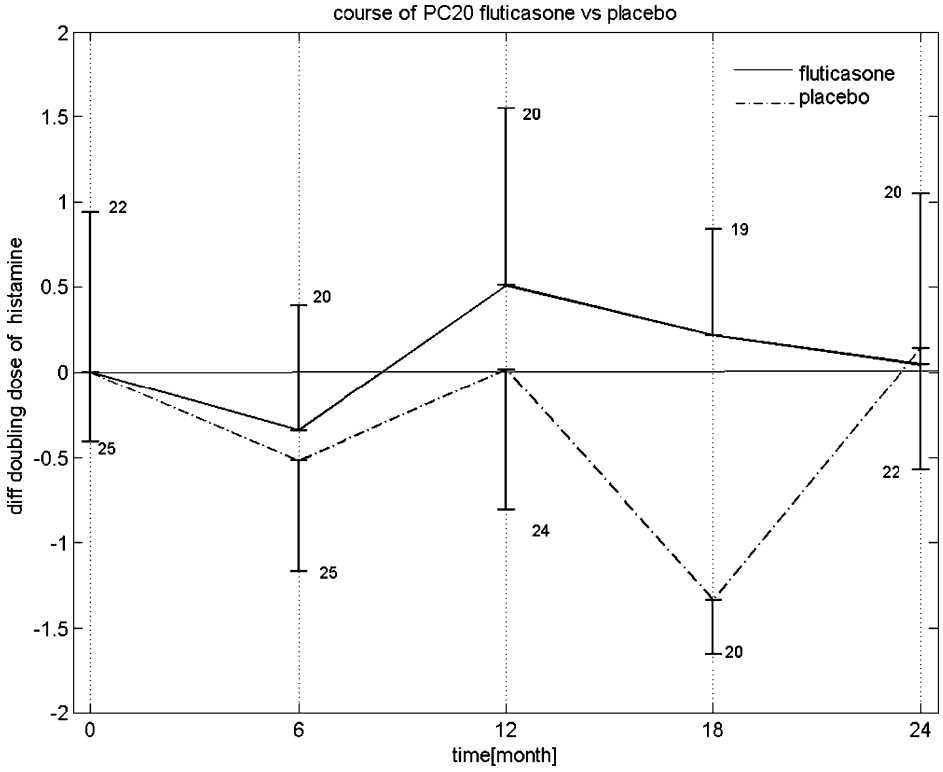

Figure 2. Mean difference in PC_{20} from baseline for each point of measurement.

a physician with asthma or COPD, with a rapid decline in lung function and signs of bronchial hyperresponsiveness. The study did not find that fluticasone significantly slowed the decrease in FEV_1 or decreased bronchial hyperresponsiveness over the study period.

The study was able to reach the targeted number of eligible subjects, but was underpowered, mainly due to refusal to participate. Reasons for this were unwillingness to get medication for (subjectively) mild symptoms and fear of steroids. This in fact hampers the effectiveness of any screening for early asthma and COPD.

Other studies showed markedly beneficial effects of early steroid intervention in steroid-naïve patients with asthma (1,5,6). However, these studies concerned treatment of patients who had been diagnosed in regular care, and undertreatment might be an explanation for the results found. This study was unable to differentiate between asthma and COPD as it was directed at their preclinical stage.

In conclusion, in this study, steroid-naïve subjects with a rapid decline in FEV_1 did not benefit from fluticasone 250 μg b.i.d. compared to a placebo treatment, but the study remains inconclusive due to being underpowered.

References

1. Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. Am Rev Respir Dis 1993;139:806–17.
2. Dompeling E, van Schayck CP, van Grunsven PM, van Herwaarden CLA, Akkermans RPM, Molema J, et al. Slowing the deterioration of asthma and chronic obstructive pulmonary disease observed during bronchodilator therapy by adding inhaled corticosteroids. A 4-year prospective study. Ann Intern Med 1993;118:770–8.
3. van den Boom G, Rutten-van Molken MPM, Tirimanna PRS, van Schayck CP, Folgering HTM, van Weel C. Association between health-related quality of life and consultation for respiratory symptoms: results from the DIMCA programme. Eur Respir J 1998;11:67–72.
4. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8: 1398–420.
5. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994; 331:700–5.
6. O'Byrne PM, Cuddy L, Taylor DW, Birch S, Morris J, Syrotuik J. Efficacy and cost benefit of inhaled corticosteroids in patients considered to have mild asthma in primary care. Can Respir J 1996;3:169–75.