Eur Respir J
1988, 1, 22–26

Moderately severe chronic airflow obstruction. Can corticosteroids slow down obstruction?

D.S. Postma*, I. Peters**, E.J. Steenhuis***, H.J. Sluiter*

Moderately severe chronic airflow obstruction. Can corticosteroids slow down obstruction? D.S. Postma, I. Peters, E.J. Steenhuis, H.J. Sluiter.

ABSTRACT: In a former study in patients with severe chronic airflow obstruction (CAO), (forced expiratory volume in one second (FEV_1) ranging from 350–910 ml), we concluded that daily oral corticosteroids might slow down the progression of disease. The results of the present long-term (14–20 yr) study on 139 non-allergic patients with less severe CAO ($FEV_1 \geq 1200$ ml, FEV_1 as a percentage of vital capacity (FEV_1%VC) 40–55%) confirm and extend our former observations. Four patterns of the course of FEV_1 and inspiratory vital capacity (VC) in time were recognized: 1) linear decrease; 2) no change; 3) initial increase, followed by decrease; 4) initial decrease, followed by increase. Groups 1 and 3 had a higher functional residual capacity as a percentage of total lung capacity (FRC%TLC) as compared to group 2 and 4; the work of breathing was lower in group 2 than in the other three groups. Otherwise the initial 82 parameters, including the degree of reversibility of airflow obstruction and smoking habits were comparable in the four groups. The four patterns of FEV_1 showed a strong association with the long-term use of prednisolone. When oral prednisolone was instituted or increased to a dose of at least 10 mg/day continuously, FEV_1 either remained constant, decreased more slowly or even increased over many years of follow-up. When the oral dose was diminished to below 10 mg/day, FEV_1 decreased. The results of this retrospective (uncontrolled) study again suggest that the long-term use of oral prednisolone, in a dose of above 7.5 mg/day, may slow down progression of disease in CAO, both in patients with 'irreversible' and partly reversible airflow obstruction.

Eur Respir J. 1988, 1.

* Department of Pulmonology, (and Statistician**), University Hospital, Groningen.
*** Asthma Clinic, Beatrixoord, Haren, The Netherlands.

Correspondence address: D.S. Postma, M.D., Department of Pulmonology, University Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands.

Keywords: Chronic airflow obstruction; corticosteroids; long-term therapy.

Chronic airflow obstruction (CAO) is generally believed to be an unremittingly progressive disease. Except for the fact that oxygen may alter the course and prognosis [1], it has been difficult to demonstrate the usefulness of any other specific form of therapy in producing an objective change in the progression of the disease or in survival [3, 11].

In a former, retrospective, study in patients with very severe airflow obstruction [14], we showed that the long-term use of prednisolone was associated with survival and a slowing of the decline of forced expiratory volume in one second (FEV_1). After stopping the prednisolone, or decreasing the dose below 10 mg/day, FEV_1 continued to decline.

These patients had very severe CAO, FEV_1 ranging from 350–910 ml (mean ± SD: 0.61 ± 0.31 *l*). The present study on 139 patients with less severe airflow obstruction ($FEV_1 \geq 1200$ ml) confirms the observations mentioned above on the possible beneficial influence of prednisolone on the course of the FEV_1.

Patients and methods

All patients meeting the following criteria were included in the investigation: 1) referral because of symptoms and signs of CAO; 2) first clinical observation for CAO between January 1, 1964 and December 31, 1972; 3) FEV_1 equal to or higher than 1200 ml; 4) FEV_1 as a percentage of the inspiratory vital capacity (VC), between 40 and 55%, increase on bronchodilation $\leq 15\%$; 5) no allergy, <2 positive skin tests and eosinophils $<300/mm^3$; 6) first clinical observation in a stable phase of the disease; 7) regular out-patient clinic visits after the first observation; 8) no other known progressive or life-limiting disease.

The first observation period included careful recording of history, physical examination, chest radiography, and a 12-lead electrocardiogram. Lung function studies included VC, FEV_1, forced inspiratory volume in one second (FIV_1) and maximal breathing capacity (MBC) (Lode D53R spirometer). Residual volume (RV) was determined by the closed-circuit helium-dilution method. Total lung capacity (TLC) was calculated as the sum of VC and RV. The pulmonary nitrogen wash-out rate was determined with a nitrogen analyser. Blood gas tensions at rest were measured with Radiometer membrane electrodes. Volume-Pressure (V-P) diagrams of the lungs were made using an intra-oesophageal balloon; compliance and viscous work of breathing were calculated from V-P diagrams. Predicted values for

lung volumes and lung mechanics were those of TAMMELING [17] and HILVERING [5].

Reversibility of bronchial obstruction was tested using thiazinamium (Multergan®), a bronchodilator with markedly anticholinergic properties [2, 6]; VC, FEV_1, and work of breathing were calculated before and 30 min after intramuscular injection of 25 mg of thiazinamium. Bronchial hyperreactivity was tested using inhalation of aerosolized histamine in stepwise increasing concentrations [4].

After the initial investigation, all 139 patients were treated with a variable combination of anticholinergics (86%), theophyllins (88%), and sympathomimetics (12%). From 1964–1968, oral prednisolone was administered (10 mg/day in women and 15 mg/day in males), unless severe hypertension, recurrent duodenal ulcers, far-advanced osteoporosis, or diabetes existed. After 1968, long-term oral corticosteroid treatment was gradually abandoned because of the side-effects and the introduction of the inhalation corticosteroids.

The course of the lung function was determined by linear and squared regression of obtained FEV_1 and VC values against time. Groups were arranged according to the squared multiple correlation coefficients, measuring the amount of variance explained by the model, in linear and squared regression as previously reported [14]. Divisions made in this way were clear-cut, standard deviations of the squared correlation coefficients being small.

Data of lung function at follow-up (mean: 3.5 values per patient per year) were included in the investigation only if the patient was in a stable phase, *i.e.* with no acute exacerbation in the last month before measurement. Maintenance therapy was continued throughout the examination. In patients who died in hospital, autopsy was generally performed; in other cases clinical data or information from the general practitioner were obtained to ascertain the cause of death.

After processing by computer, the data were analysed by the Student's t-test and the chi-square test. The degrees of significance were $p<0.05$ or lower, two-sided. Correlation coefficients were determined by linear regression analysis.

Results

Mean duration of follow-up was 10.6 ± 3.8 yr, ranging from 2.8–20 yr. Some characteristics of the 139 patients, including per cent predicted values for spirometric variables, are shown in table I. All together, 82 initial variables were tested; only six patients missed two variables. No loss of patients during follow-up occurred.

Forty two patients died (30%); the causes of death are presented in table II. Only four patients (9.5% of all deaths) died from a cardiorespiratory cause. The differences between the patients who died and who were still alive at the end of the study (January 1984), are smoking habits (85% and 70% being smokers

Table I. - Initial characteristics of the study group (n=139)

	Mean ± SD
Age, years	48.3 ± 8.3
Male, %	83.0
Smokers, %	75.0
Ex-smokers, %	20.0
FEV_1, %predicted	62.7 ± 12.8
FEV_1, ml	1880.0 ± 433.0
FEV_1, %VC	47.6 ± 4.0
FEV_1, %VC pb	53.7 ± 4.2
FIV_1 %predicted pb	100.9 ± 20.0

pb: post bronchodilator

Table II. - Causes of death in all patients (n=42)

Cause of death	Number	%
Cardiorespiratory	4	9.5
Sudden unexplained	1	2.4
Neoplasm - Pulmonary	15	35.7
- Other	5	11.9
Cerebrovascular accident	2	4.8
Postoperative death	2	4.8
Acute myocardial infarction	15	30.9

respectively, $p<0.05$) and the absolute FEV_1 (1.88 ± 0.30 *l* and 1.65 ± 0.29 *l* respectively, $p<0.05$). FEV_1% predicted, however, was not significantly different between the two groups. All other parameters were comparable in the two groups.

Four distinct patterns in the course of FEV_1 and VC are apparent: (fig. 1) 1) linear decrease (LIN), 81 patients (64%); 2) no significant increase or decrease at follow-up (no change = NCH), 18 patients (14%); 3) initial increase followed by decrease ('convex' = CON+), 12 patients (10%); 4) initial decrease followed by increase ('concave' = CON−), 15 patients (12%). Some characteristics of the four groups are presented in table III. The LIN and CON+ groups had a significantly higher FRC%TLC after bronchodilation as compared to the NCH and CON− groups. The work of breathing was signifi-

Table III. - Initial characteristics in the LIN, NCH, CON+, and CON– group

	LIN	NCH	CON+	CON–
number	81	18	12	15
age, year	48 ± 9	51 ± 7	46 ± 9	49 ± 7
smokers, %	70	61	77	71
FRC%TLC pb	54 ± 7***	51 ± 7	56 ± 7***	49 ± 11
FEV_1, ml	1900 ± 443	1721 ± 431	1911 ± 408	1718 ± 385
FEV_1 %predicted	63 ± 12	61 ±16	64 ± 11	61 ± 14
ΔFEV_1, %initial	29 ± 14	31 ±10	31 ± 12	35 ± 19
ΔFEV_1, %pred–in	47 ± 39	56 ± 28	59 ± 28	57 ± 38
C_{sp}pb, l/cmH_20	0.75 ± 0.40	0.58 ± 0.23	0.59 ± 0.23	0.71 ± 0.26
Work of breathing	51 ± 23	36 ±18*	55 ± 25	57 ± 57
FEV_1/FIV_1 pb, %	67 ± 11	71 ± 9	69 ± 11	71 ± 10
time of follow-up, months	129 ± 40	130 ± 49	123 ± 21	139 ± 56
%time < 10 mg	97 ± 9**	29 ± 41*	56 ± 19	69 ± 32
% time 0 mg	91 ± 25**	27 ± 29*	58 ± 38	47 ± 41

ΔFEV_1: change in FEV_1 after intramuscular administration of 25 mg thiazinamium; ΔFEV_1%(pred–in): ΔFEV_1 as a percentage of the predicted minus prebronchodilator FEV_1; C_{sp} pb: specific compliance after bronchodilation; FEV_1/FIV_1 pb: FEV_1 divided by one sec. forced inspiratory volume after bronchodilation; %time=the percentage of total follow-up time that <10 mg or 0 mg of prednisolone has been used. * significantly lower as compared to LIN, CON–, and CON+ group; ** significantly higher as compared to NCH, CON–, and CON+ group; *** significantly higher as compared to NCH, and CON– group.

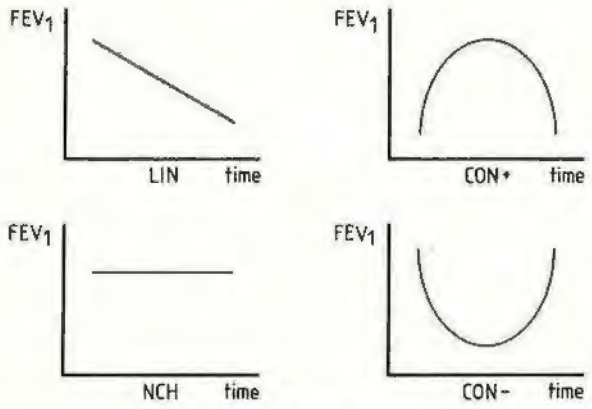

Fig. 1. Patterns of decline of FEV_1. LIN: linear decrease; CON+: convex; CON−: concave; NCH: no change.

cantly lower in the NCH group than in the other groups. Otherwise, the four groups were comparable in initial characteristics, *e.g.* age, initial FEV_1 level (both absolute and as percentage predicted), degree of aspecific bronchial hyperreactivity, blood gases, or reversibility in FEV_1 and VC on bronchodilation. In each group some patients showed 'irreversible' airflow obstruction (increase of FEV_1 as percentage of prebronchodilator value <20%); 20 patients in the LIN group (25%); 5 in the NCH group (28%); 3 in the CON+ group (25%); and 5 in the CON− group (33%).

Effect of therapy

Therapy in the form of anticholinergics, theophylline, beta-2-sympathomimetics, and antibiotics was virtually similar in the four groups of patients.

The only significant difference between the groups was the long-term use of corticosteroids *i.e.* prednisolone *per os*. Daily treatment with oral prednisolone (>9 months consecutively during the period of observation, in a dosage of ≥10 mg per day) was taken by 12% of the LIN group, 81% of the NCH group, 83% of the CON+, and 100% of the CON− group. The duration taking <10 mg prednisolone daily, expressed as a percentage of the total time that

each patient was surveyed, was in the same groups: 97±9% (mean±SD); 29±41%; 56±19%; and 69±32% respectively (table III).

In the LIN group, the decrease in FEV_1 per year was 78±45 ml (mean±SD). The 12% of patients who used ≥10 mg of prednisolone daily for a shorter period of follow-up (10–55 months, 6–29% of total time of follow-up (n=10)), showed a decrease in FEV_1 of 42±12 ml per year, the other 71 patients revealed a decrease of 82±46 ml ($p<0.05$). In the same ten patients who did use prednisolone, there was a significant correlation between the duration of follow-up that prednisolone was used, and the decrease of FEV_1 per year ($r=0.71$, $p<0.05$). No differences in initial characteristics between these two subgroups were found.

In the NCH group, six of the eighteen patients did not use ≥10 mg of prednisolone during the whole period of observation. These six patients (table IV) had a significantly higher degree of reversibility of airflow obstruction, a higher initial FEV_1, as a percentage of the predicted value after bronchodilation, and a higher percentage of non-smokers, as compared to the other twelve patients of the NCH group and the 71 patients in the LIN group who did not use daily prednisolone. Otherwise the patients were comparable in initial characteristics. The other twelve patients in the NCH group all used ≥10 mg prednisolone during the whole period of follow-up.

In the CON+ group, reduction of prednisolone to 7.5 mg or less was always followed by a decrease in FEV_1. One patient took only 7.5 mg prednisolone per day, but nevertheless his FEV_1 increased over 4 yr of follow-up. He started smoking again and stopped medicine, subsequently the FEV_1 decreased significantly. When this patient is omitted from the group, there is a significant correlation between the moment of reduction of prednisolone to 7.5 mg per day or lower and the time of decrease in FEV_1 ($r=0.57$, $p<0.05$).

In the CON− group no prednisolone at all or <10 mg per day was used during the time that FEV_1 decreased; when prednisolone was instituted or increased over 7.5 mg per day, however, FEV_1 always increased. There is a strong correlation between the moment of start of increase of prednisolone to 10 mg per day, and the time of increase of FEV_1 ($r=0.80$, $p<0.001$).

Thirteen patients were excluded from this study; five patients because of fewer than seven values of FEV_1 at follow-up, and eight because the course of the FEV_1 and VC were discongruent (*e.g.* FEV_1 linear increase and VC no change). In these eight patients, the course of lung function however, always correlated with the use of prednisolone. No significant differences between the initial parameters of these patients and the other 126 patients were found.

Table IV. - Initial characteristics of 6 patients in the NCH group who did not use ≥10 mg prednisolone continuously, compared with the rest of the NCH group and patients in the LIN group who never used prednisolone.

	NCH never or temporary steroids	NCH always steroids	LIN no steroids
Number of patients	6	12	71
FEV_1, %predicted, pb	79 ± 14*	67 ± 19	69 ± 1
ΔFEV_1%initial	36 ± 8*	27 ± 10	28 ± 14
% smokers	0	38	23
% ex-smokers	100	62	77

FEV_1%predicted pb: FEV_1 after bronchodilation as a percentage of the predicted value; ΔFEV_1%initial: increase of FEV_1 after bronchodilation as a percentage of the prebronchodilator value.
* significantly different from other two groups.

Discussion

The results of this study in 139 patients with CAO are in accordance with the outcome of a previous study [14], *viz.* that the use of prednisolone is associated with a beneficial effect on the course of FEV_1. In the former study [14] in patients with a very low initial FEV_1 (mean value 0.61 *l*), three patterns of FEV_1 in the time were recognized; LIN, CON+ and NCH. These patterns showed a strong association with the long-term use of prednisolone. When the daily dosage of prednisolone was less than 10 mg, the FEV_1 decreased continuously. The same pattern in course of FEV_1 and VC and the same association with the use of prednisolone was found in the present study. Moreover, this study includes a group of patients with an initial decrease of FEV_1, followed by an increase (CON−). The strong significant correlation between the institution, or increase of oral prednisolone dose to ≥10 mg/day and the increase in FEV_1, corroborates the former observation that prednisolone may slow down the progression of disease. The finding that those patients in the LIN group who used corticosteroids for only a few months, had a slower decrease of FEV_1 in time as compared with the patients who did not use corticosteroids at all, also strongly suggests the influence of prednisolone on the progression of the disease.

Selection of the patients may have influenced the outcome of this study. Patients with CAO who will benefit most from short term courses of corticosteroids seem to be those with more reversibility of airway obstruction on bronchodilation [8, 10], eosinophilia, and atopy [15, 16], and those with wheezing as a predominant symptom [10, 15]. We carefully selected a group of patients without atopy or eosinophilia: the initial degree of obstruction was in a

narrow range, FEV_1%VC, 40–55%. In these patients repeated history taking did not reveal any asthmatic attack or wheezing as a predominant symptom. The degree of reversibility of airflow obstruction was comparable in the four groups; each group included about 25% patients with 'irreversible' airflow obstruction. Thus the beneficial effect of long-term treatment with prednisolone is at variance with the short-term effect [8, 10] in that it occurs both in patients with 'irreversible' (<20% increase of FEV_1 from prebronchodilator level at that particular moment) and reversible airflow obstruction. This has also been noted by MITCHELL *et al.*, in a study with 40 mg of prednisolone for 14 days, in 43 patients with CAO [9].

Corticosteroids are known to reduce vascular permeability, oedema formation and inflammatory reaction to infection. KRAAN *et al.* [7] recently showed a beneficial effect of a 4-weeks course of inhalation steroids on airway hyperreactivity. This may also play a role in our study.

Our study included six patients who did not show a decrease in FEV_1, although they did not use ≥10 mg of prednisolone during the total period of the follow-up. The combination of a higher degree of reversibility, a higher FEV_1% predicted after bronchodilation, and the fact that all six were ex-smokers, is in accordance with our previous findings that these factors are related to a better prognosis [12, 13]. We do not know, however, what would have happened to the course of FEV_1 if these patients had been treated with prednisolone.

Our conclusions are based on a retrospective analysis. We did not have a control group; patients in the CON+ and CON− group, however, might be regarded as their own control. The beneficial effect of prednisolone is similar in patients with CAO and a very low initial FEV_1 (0.61 *l*), as well as in patients with a higher initial FEV_1 (1.9 *l*) and applies as well to patients with partly reversible compared to those with 'irreversible' airflow obstruction.

In the light of the current knowledge about side-effects, it is clearly not advisable to start oral prednisolone in a dose of 10 mg/day in all patients with CAO. A prospective controlled study, in which both the combination of oral and inhalation corticosteroids and inhalation corticosteroids alone are used, is in progress.

Acknowledgements: This investigation was made possible by a grant from the Netherlands Astma Fund. We wish to thank U. Bosma for her skilful typing.

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RÉSUMÉ: Dans une étude antérieure portant sur des malades atteints d'obstruction chronique des voies aériennes (CAO) sévére FEV_1 compris entre 350 et 910 ml nous avons conclu que l'administration orale quotidienne de glucocorticoïdes était capable de ralentir la progession de la maladie. L'étude longitudinale actuelle (suivi de 14 à 20 ans) porte sur 139 patients non allergiques avec une CAO moins sévére (FEV_1 >1200ml, avec FEV_1/VC compris entre 40 et 55%) confirme et étend nos observations antérieures. Quatre types d'évolution du FEV_1 et de la capacité vitale inspiratoire au cours du temps ont été identifiés: 1) diminution linéaire 2) pas de changement 3) augmentation initiale, suivie de diminution 4) diminution initiale, suivie d'augmentation. Dans les groupes 1) et 3) le rapport FRC/TLC est plus élevé que dans les groupes 2) et 4); le travail ventilatoire est plus bas dans le groupe 2 que dans les autres groupes. Par ailleurs les 82 indices initiaux mesurés, y compris le degré de réversibilité de l'obstruction bronchique et le tabagisme, étaient comparables dans les quatre groupes. Les quatre types d'évolution du FEV_1 sont en association étroite avec l'utilisation au long cours de prednisolone. Lorsque la dose orale quotidienne atteint au moins 10 mg, FEV_1 soit reste constant, soit diminue plus lentement, voire même augmente après plusieurs années de suivi. Lorsque la dose est inférieure à 10 mg, FEV_1 diminue. Les résultats de cette étude rétrospective non contrôlée suggérent à nouveau que l'administration prolongée de prednisolone par voie orale, à une dose quotidienne supérieure à 7,5 mg, est susceptible de freiner l'évolution de la maladie en cas de CAO, aussi bien chez les malades avec une obstruction 'irréversible' que chez eux avec une obstruction partiellement réversible.