Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? The Dutch CNSLD Study Group. The Dutch Chronic Nonspecific Lung Disease Study Groups

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Chest 1996;110;35-41

Is Delayed Introduction of Inhaled Corticosteroids Harmful in Patients With Obstructive Airways Disease (Asthma and COPD)?*

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Background: **The institution of inhaled corticosteroids is generally advocated for effective treatment of patients with asthma. It is yet unknown what is the best time to start inhaled corticosteroid therapy and especially whether delayed introduction is harmful.**
Phase 1: **In a previous study in patients with asthma and COPD, we found that 2.5 years of treatment with a β_2-agonist plus inhaled corticosteroid (BA+CS) was more effective in improving the FEV_1 and the provocative concentration of histamine causing a 20% reduction in FEV_1 (PC_{20}) than treatment with a β_2-agonist plus anticholinergic (BA+AC) or placebo (BA+PL).**
Phase 2: **We extended this study with 6 months to investigate whether delayed introduction of inhaled CS therapy (800 µg beclomethasone dipropionate) in the groups previously not treated with inhaled CS (BA±AC) could also improve FEV_1 and PC_{20} to the same degree. A distinction was made between patients with predominantly asthma (high baseline reversibility, $\Delta FEV_1 \geq 9\%$ of predicted), and predominantly COPD (low baseline reversibility, $\Delta FEV_1 < 9\%$ of predicted).**
Results: **Improvement of FEV_1 percent predicted by inhaled CS was comparable both in the asthmatics between phase 1 (13.8% predicted) and phase 2 (8.5% predicted; p=0.13) as well as in the patients with COPD (2.5% and 1.5% predicted, respectively). PC_{20}, however, increased significantly more in the asthmatics in phase 1 (1.77 doubling concentration [DC]) than in phase 2 (0.79 DC; p=0.03). Improvement of PC_{20} in the patients with COPD was not significantly higher in phase 1 (0.74 DC) than in phase 2 (0.00 DC; p=0.19).**
Conclusions: **Our study indicates that although delayed introduction of inhaled CS in asthmatics leads to similar improvements in FEV_1, improvements in PC_{20} are significantly less. These findings in patients with longer-existing asthma concur with other findings in newly detected asthma. We suggest that institution of inhaled CS therapy should not be postponed in asthmatics with documented airways obstruction and reversibility.** ***(CHEST 1996; 110:35-41)***

Key words: airway hyperresponsiveness; asthma; COPD; inhaled corticosteroids; lung function

Abbreviations: BA+AC=β_2-agonist plus anticholinergic; BA+CS=β_2-agonist plus inhaled corticosteroid; BA+PL=β_2-agonist plus inhaled placebo; CI=confidence interval; CS=corticosteroid; DC=doubling concentration; ICS=inhaled corticosteroids; $MEF_{50\%}$=maximal forced expiratory flow at 50% of the actual FVC; PC_{20}=provocative concentration of histamine causing a 20% reduction in FEV_1; RSD=residual standard deviation; RV=residual volume; TLC=total lung capacity

Inhaled corticosteroids (ICS) have been demonstrated to be effective in improving symptoms, airways hyperresponsiveness, and airways obstruction in patients with asthma.[1-9] It is unclear, however, when ICS therapy should be started in early or mild disease. Current guidelines advocate the timing of institution to be dependent on the amount of bronchodilators daily used.[10-12] This may vary considerably among patients, because there are marked differences in individual perception of breathlessness,[13-15] probably leading to differences in the amount of bronchodilators used. Moreover, this recommendation is not based on studies comparing the effects of delayed vs early institution. It is conceivable that delayed institution could lead to the irreversible lung function loss that some patients with asthma demonstrate.[16] This question is especially important given the suggestion that continuous use of

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This study was supported by a grant from the Netherlands' Health Research Promotion Program (SGO). We acknowledge the support from three pharmaceutical companies who supplied the study medication in identical metered-dose inhalers: Astra Pharmaceuticals, Boehringer Ingelheim, and Glaxo.
†A list of the members of the Dutch CNSLD Study Group is located in the Appendix.
Manuscript received October 5, 1995; revision accepted February 14, 1996.

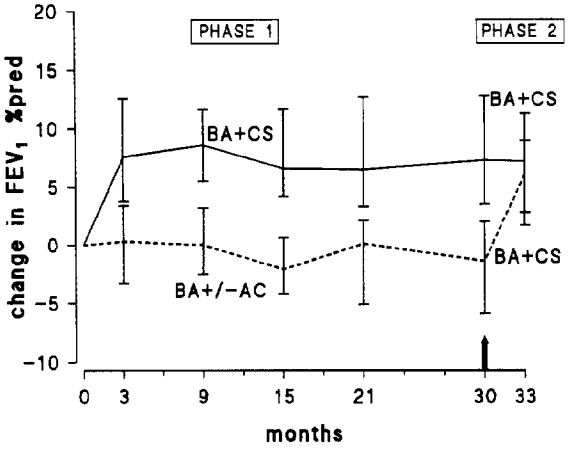

FIGURE 1. Change in FEV_1 (%pred) for all patients followed up for at least 33 months. Treatment was changed at 30 months (solid arrow). In the present study, only changes in phase 1 (0 to 3 months) and phase 2 (30 to 33 months) are compared. Medians and 95% CIs are presented.

bronchodilators without ICS leads to accelerated decline in lung function.[17]

The value of ICS in patients with COPD is currently unclear. Short-term studies have not shown a beneficial effect.[18-20] A few long-term reports suggest that ICS therapy slows down the progressive deterioration of lung function in at least some patients with COPD.[7,9,21-23] Here again, the effect of delayed institution of ICS therapy is uncertain.

The present study was designed to investigate whether a 2.5-year delay of ICS administration leads to smaller improvements in FEV_1 and airways hyperresponsiveness in patients with mild to moderately severe obstructive airways disease (asthma and COPD).

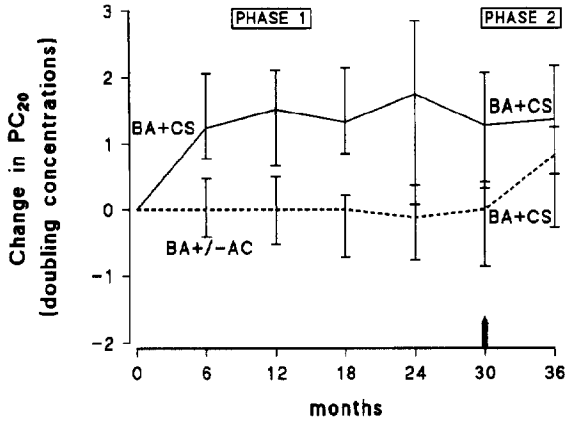

FIGURE 2. Change in $\log_2 PC_{20}$ for all patients followed up for at least 36 months. Treatment was changed at 30 months (solid arrow). In the present study, only changes in phase 1 (0 to 6 months) and phase 2 (30 to 36 months) are compared. Medians and 95% CIs are presented.

MATERIALS AND METHODS

The current investigation is an extension of a 2.5-year multicenter study.[7] Patients aged 18 to 60 years with mild to moderately severe obstructive airways disease (asthma and COPD) were selected from 6 university outpatient clinics if they met the following 2 criteria: (1) a concentration of histamine causing a 20% decrease in FEV_1 (PC_{20}) of 8 mg/mL or less[24,25]; and (2) baseline FEV_1 more than 1.2 L and 1.64 to 4.5 residual standard deviations (RSD) below the predicted value, or the FEV_1/inspiratory vital capacity ratio more than 1.64 RSD below the predicted value, provided that total lung capacity (TLC) was higher than 1.64 RSD below the predicted level.[7] Patients with conditions or medication likely to interfere with the purpose of the study were excluded. Further details of the study methods have been described elsewhere.[24]

Study Design

The study consisted of two parts as depicted in Figures 1 and 2.

Phase 1: Two hundred seventy-four patients were randomly allocated to 1 of 3 double-blind treatment regimens: all patients received from identical metered-dose inhalers an inhaled β_2-agonist (terbutaline, 250 µg, 2 puffs qid) combined with either an ICS (beclomethasone, 100 µg, 2 puffs qid [BA+CS]), or an inhaled anticholinergic (ipratropium bromide, 20 µg, 2 puffs qid [BA+AC]), or an inhaled placebo 2 puffs qid (BA+PL). Additional bronchodilator medication was supplied as salbutamol dry powder inhalations (400 µg) on demand. No other concomitant pulmonary medication was allowed, except during exacerbations, when a 12-day course of oral prednisolone therapy was prescribed. Follow-up visits were scheduled every 3 months during 2.5 years, at which the level of airways obstruction and, at alternate visits, PC_{20} were measured.

Phase 2: All patients of group BA+AC and BA+PL who had completed phase 1 and were willing to participate in phase 2 were switched after 2.5 years to the same treatment the BA+CS group had been receiving from the start of phase 1: beclomethasone (100 µg, 2 puffs qid) combined with terbutaline (250 µg, 2 puffs qid). The BA+CS group continued treatment with their medication. The reallocation of medication was performed in a double-blind fashion, *ie*, the prior code was not broken for patients or their physicians. By design, however, it was clear to all patients that from the start of phase 2, they were all treated with ICS. Informed consent was obtained from all patients. The level of airways obstruction was measured at baseline and 3 months after the start of phase 2, whereas PC_{20} was measured at baseline and after 6 months.

Lung Function

FEV_1 and PC_{20} were measured only during clinically stable periods, and not within 4 weeks after the end of a prednisolone course. Eight hours before these tests, treatment with all pulmonary medication was discontinued. FEV_1 was measured using water-sealed spirometers until at least 3 reproducible (<5% difference) recordings were obtained; the highest value was then used for analyses. Reference values are those of the European Community for Coal and Steel.[25] For bronchodilator response testing, FEV_1 was measured before and 20 min after 4 separate inhalations of 250 µg of terbutaline sulfate from a metered-dose inhaler, administered through a 750-mL spacer device (Nebuhaler; Astra Pharmaceuticals; Rijswijk, the Netherlands). Reversibility was expressed as percent predicted normal.[26] Residual volumes (RV) and TLC were measured with the closed circuit helium dilution method[25] and the expiratory flow at 50% of the actual FVC ($MEF_{50\%}$) was derived from a maximal expiratory flow volume curve, using a pneumotachometer. Histamine provocation tests were performed using a 2-min tidal breathing method.[27] For analysis purposes, patients already responding to saline solution or to the lowest concentration of histamine (0.03 mg/mL) were assigned a PC_{20} value of 0.015,

Table 1—*Baseline Characteristics (Means±SD) at the Start of Phase 1 and Phase 2*

	Start Phase 1		Start Phase 2
	BA+CS* (n=91)	BA±AC (n=183)	BA+CS† (n=76)
Age, yr	40.2 (12.3)	39.2 (12.1)	42.1 (12.2)
Sex, M/F	59/32	117/66	55/21
FEV_1, %pred	64.6 (15.4)	63.3 (15.3)	61.7 (15.8)
FEV_1/VC, %	56.5 (11.5)	54.7 (10.8)	53.0 (11.6)
ΔFEV_1, %pred‡	11.3 (8.6)	12.3 (9.0)	13.6 (9.9)
$MEF_{50\%}$, %pred	35.3 (14.8)	33.4 (14.7)	29.8 (13.4)
RV/TLC, %pred§	118.3 (24.7)	118.9 (24.4)	117.5 (24.5)
$\log_2 PC_{20}$, mg/mL‖	−1.62 (2.23)	−2.11 (2.32)	−1.81 (2.66)
Geometric mean PC_{20}, mg/mL	0.33	0.23	0.29
Atopic, %	56.0	55.7	56.6
Current smoker, %	36.3	35.5	34.2

*Treated with BA+CS at the start of phase 1 (0 to 3 months).
†Treated with BA+CS only from the start of phase 2 (30 to 33 months).
‡ΔFEV_1, %pred=bronchodilator response to β_2-agonist (terbutaline, 1,000 μg).
§RV/TLC=ratio of residual volume and total lung capacity.
‖$\log_2 PC_{20}$=base 2 logarithm of provocative concentration of histamine producing a fall of 20% in FEV_1.

being half the lowest concentration applied.[24] Patients refrained from drinking tea or coffee and from smoking between measurements.

Symptom Scores

After instruction at the outpatient clinic, symptom scores were noted daily at home for 14 consecutive days before every visit to the clinic on a 4-point scale (0=no symptoms; 3=severe symptoms) for wheeze, dyspnea, cough, and phlegm, separately. Symptom scores over 14 days were averaged for each of the symptoms and then added to obtain a mean symptom score (up to a maximum of 12).

Classification of Patients

A distinction was made between those patients with high reversibility (ΔFEV_1 ≥9% of predicted) considered as having predominantly asthma, and those with low reversibility (ΔFEV_1 <9% of predicted) considered as having predominantly COPD. Patients were categorized as atopic on the basis of skin prick testing.[7]

Statistical Analysis

Data are presented as medians (plus 95% confidence interval [CI] of the median) unless stated otherwise. All calculations with PC_{20} were performed using the base-2 logarithm, 1 unit difference reflecting 1 doubling dose. Because no significant differences were found between the BA+AC and BA+PL groups with regard to FEV_1 and PC_{20} during phase 1 both at baseline and in response to their respective treatments,[7] the data of these groups were subsequently pooled for analysis during phase 2. Reversibility was measured both in phase 1 and 2 at baseline and used for patient classification. Improvement with therapy was assessed as change from baseline of phase 1 in the group receiving corticosteroid (CS) from the start of the study and in the group receiving CS only from the start of phase 2 as change from baseline of phase 2. Mann-Whitney *U* tests were employed and p values <0.05 were considered significant.

Results

Of the 274 patients randomised in phase 1, 101 patients were withdrawn before the end of the study. The withdrawal rate was significantly larger in the BA+PL and BA+AC groups (44 and 45 patients, respectively) than in the original BA+CS group (12; p<0.0001). Seventy percent of this withdrawal was related to an increase in pulmonary symptoms.[7] Of the remaining 94 patients not treated with ICS in phase 1 (47 in both the BA+AC and BA+PL group), 76 agreed to continue in phase 2. Baseline characteristics of all patients at the start of phase 1 (Table 1) were comparable among the original BA+CS, BA+AC, and BA+PL groups.[7] There were no significant differences in baseline characteristics between the group originally treated with BA+CS and the group treated with BA+CS only in phase 2. When the baseline characteristics of the patients treated with BA+CS in phase 2 only were compared between the start of phase 1 and phase 2, the $MEF_{50\%}$ had significantly deteriorated (p=0.02), but not FEV_1 and PC_{20}.

Table 2 shows the characteristics of the patients subdivided in asthma and COPD according to reversibility. In phase 1, 49 patients in the BA+CS group had high reversibility (ΔFEV_1 to terbutaline ≥9% of predicted, considered to have predominantly asthma) and 42 had low reversibility (ΔFEV_1 <9% of predicted, considered to have predominantly COPD). In phase 2, 53 patients had high reversibility and 23 had low reversibility. There were no significant differences between the baseline characteristics of the asthmatic groups at the start of phase 1 and 2 or between the COPD groups.

There was a median rise in FEV_1 of 8.6% predicted (95% CI, 4.9 to 12.6) in the group treated with BA+CS at the start of phase 1 (0 to 3 months), compared with 4.5% predicted (95% CI, 1.8 to 10.0) in the group receiving CS only from the start of phase 2 (30 to 33 months). This difference was not significant (p=0.24).

Table 2—*Baseline Characteristics (Means±SD) of the Groups Receiving ICS at the Start of Phase 1 and 2, With a Subdivision in Patients With High Reversibility (≥9% Predicted) and Low Reversibility (<9% predicted)

	Start Phase 1		Start Phase 2	
	High Reversibility (n=49)	Low Reversibility (n=42)	High Reversibility (n=53)	Low Reversibility (n=23)
Age, yr	36.8 (11.9)	44.2 (11.7)	37.7 (12.6)	43.9 (10.6)
Sex, M/F	26/23	33/9	34/19	21/2
FEV_1, %pred	64.6 (14.1)	64.5 (17.0)	61.2 (15.6)	70.8 (14.6)
FEV_1/VC, %	55.4 (8.4)	57.9 (14.2)	54.0 (10.7)	56.7 (10.7)
ΔFEV_1, %pred	17.5 (6.5)	4.0 (3.5)	16.6 (5.8)	4.4 (3.6)
$MEF_{50\%}$, %pred	34.9 (13.1)	35.8 (16.7)	32.7 (14.0)	37.2 (16.6)
RV/TLC, %pred	115.9 (24.7)	121.1 (24.7)	121.4 (27.4)	110.6 (24.4)
$\log_2 PC_{20}$, mg/mL	−2.35 (1.93)	−0.77 (2.30)	−2.06 (2.20)	−0.48 (2.36)
Geometric mean PC_{20}, mg/mL	0.20	0.59	0.24	0.72
Atopy, %	67.3	42.9	66.0	34.8
Current smoker, %	32.7	42.9	24.5	56.5
Symptom score	1.9 (1.75)	3.0 (2.40)	1.5 (1.38)	2.8 (2.16)

*Abbreviations as in Table 1.

Changes in FEV_1 percent predicted for all patients who reached phase 2 are presented in Figure 1.

Figure 3 shows the changes in FEV_1 percent predicted in the first 3 months of phase 1 and phase 2 for patients with high or low reversibility separately. In the patients with reversibility treated with BA+CS from the start of phase 1, the median rise in FEV_1 was 13.8% predicted (7.7 to 18.7) compared with 8.5% predicted (3.3 to 15.9) in those who received CS only from the start of phase 2 (p=0.13). In the patients with low reversibility treated with BA+CS from the start of phase 1, there was a median rise in FEV_1 of 2.5% predicted (−1.2 to 9.0), compared with 1.5% predicted (−2.3 to 4.8) in the group that received CS only from the start of phase 2 (p=0.50).

There was a median rise of 1.30 doubling concentrations (DC) (0.91 to 1.81) with BA+CS in phase 1 (0 to 6 months) compared with 0.52 (0 to 0.94) DC in phase 2 (30 to 36 months). This difference was significant (p=0.04). In Figure 2, the changes in PC_{20}, expressed as DC for all patients reaching phase 2, are depicted.

In Figure 4, the changes in PC_{20} during the first 6 months of treatment in phase 1 and phase 2 are presented for the asthmatic and COPD patients separately. There was a median rise of 1.77 DC (1.07 to 2.56) in the asthmatics treated with BA+CS from phase 1 as compared with 0.79 DC (0.00 to 1.44) in those who received CS only in phase 2. This difference was significant (p=0.03). In the COPD patients treated with BA+CS in phase 1, there was a median rise of 0.74 DC (0.08 to 1.39) compared with 0.00 DC (−0.77 to 0.65)

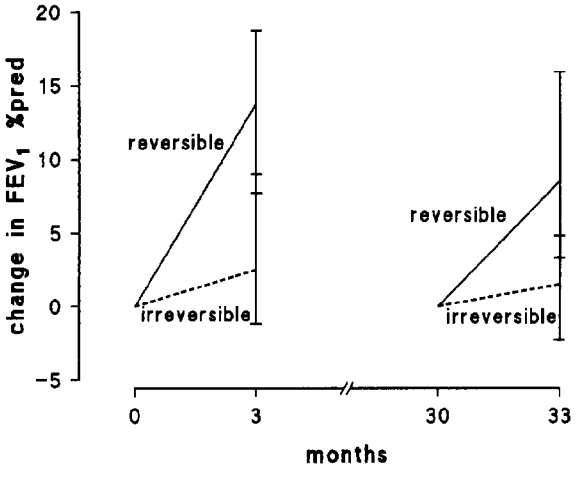

FIGURE 3. Change in FEV_1 (%pred) with ICS in the first 3 months of phase 1 and phase 2 for patients with high and low reversibility separately. Solid lines are for patients with a reversibility of 9% or more predicted (asthmatics) and dotted lines for patients with a reversibility less than 9% predicted (COPD).

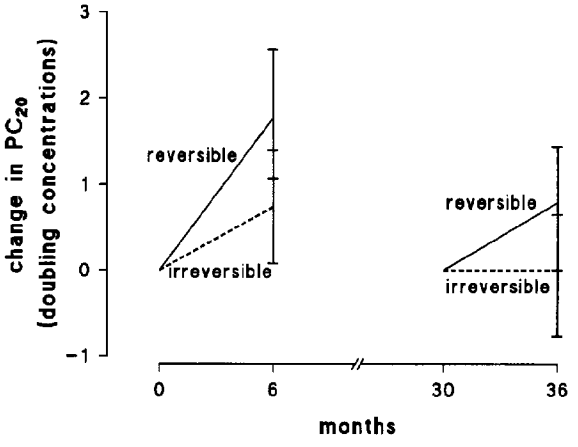

FIGURE 4. Change in PC_{20} histamine with ICS in the first 6 months of phase 1 and phase 2 for patients with high and low reversibility separately. Solid lines are for patients with a reversibility of 9% or more predicted (asthmatics), and dotted lines are for patients with a reversibility less than 9% predicted (COPD).

in phase 2 (p=0.19). Although COPD patients, as shown in Table 2, had a significantly higher mean symptom score at baseline than asthmatic patients in phase 1 and in phase 2, there was no significant difference in change in symptom scores between phase 1 and phase 2 in the 2 patient groups.

Discussion

This study suggests that a delay in the introduction of ICS therapy in patients with obstructive airways disease and marked reversibility may blunt their beneficial effect. When ICS therapy was instituted after 2.5 years of therapy with inhaled bronchodilators only, FEV_1 in asthmatics and in COPD patients improved to a similar degree as in the group that received this treatment 2.5 years earlier. Improvement of airways hyperresponsiveness, however, was smaller after delayed institution, the difference being significant only in the group with high reversibility. The difference we found in improvement in airways hyperresponsiveness between the asthmatic patients in whom ICS were administered at the start of phase 1 and those who had delayed institution might have been due to selection bias. Because the withdrawal rate in phase 1 in the groups treated with bronchodilators alone had been as high as 49%, we thought it very likely that the patients entering into phase 2 had a "survivor effect." We did not, however, find such an effect when comparing the baseline characteristics at the start of phase 1 and 2, made on the basis of those factors found to be of importance in predicting response to ICS.[7,8] Additionally, when comparing these baseline characteristics for asthmatics and COPD patients separately, no significant differences were found.

One explanation for the smaller improvement in PC_{20} in phase 2 may be ongoing airway wall inflammation in patients not having received ICS during the first 2.5 years. Airway inflammation is assumed to be an important determinant in the pathophysiologic state of asthma[28] and perhaps also in COPD.[29] CSs have potent anti-inflammatory properties,[30] such as inhibition of the release of mediators from macrophages and eosinophils and the influx of inflammatory cells into the lungs.[31] Several studies have shown beneficial effects of ICS on airways responsiveness and ventilatory function.[1,2,4-9,32,33] After delayed introduction of CS therapy, smaller increases in hyperresponsiveness can thus be expected, especially in asthmatics, in whom airway inflammation is the major feature.

Another explanation for our finding could be that bronchodilators, in the absence of CSs, have deleterious effects.[34,35] They relax smooth muscle, but do not have antiinflammatory properties. It has been suggested that they promote an increase in exposure to allergens, cigarette smoke, or other irritants.[36,37] Furthermore, hyperresponsiveness may deteriorate slightly and transiently during treatment with β-agonists only.[1,2,38] The explanation for this phenomenon is still controversial.[23,34,35] In our study, PC_{20} at baseline in phase 1 for the BA+AC groups and for phase 2 measured 2.5 years later was not significantly different from PC_{20} in the group initially treated with ICS. Furthermore, there was no significant difference in PC_{20} when the asthmatics and COPD patients were considered separately. Thus, our finding does not confirm a deleterious effect of treatment with bronchodilators only. Nevertheless, PC_{20} is an important parameter of disease in asthma, having a close relation with the degree of inflammation. ICS administration improves PC_{20}, whereas discontinuation leads to worsening of PC_{20}.[39,40]

Our findings in a group of patients with longer-existing asthma are similar to those found in a recent study by Haahtela et al[40] in a group of patients with newly detected asthma. This may suggest that the effects of late introduction of ICS therapy are not dependent on the stage of the disease. In current guidelines for the management of asthma, prescription of ICS therapy depends on the number of puffs of β_2-agonists and on symptoms. This symptom indication could conceivably lead to a later introduction of ICS therapy in certain patients. Because in our study the significant change in PC_{20} in the asthmatics was not accompanied by a change in symptom score, our findings and those of Haahtela et al[40] would question the wisdom of this aspect of the guidelines. They also suggest that lung function parameters and symptom score do provide different information about disease activity.[41]

The fact that ICS showed a more pronounced effect on FEV_1 and PC_{20}—with earlier as well as with delayed institution—in asthmatics than in patients with COPD is compatible with numerous studies in the literature showing ICS to be effective in asthma, whereas their value in COPD is still unclear.[1-9,18-23] The four-item symptom score with sputum and cough as two separate items probably favored higher reported average symptom scores in COPD. This was true for phase 1 and phase 2. The difference in change in neither of the patient groups was, however, significant between phase 1 and 2.

In conclusion, we have shown in both asthma and COPD that ICS administered in the later stages of the disease may improve FEV_1 to the same extent as when prescribed early. However, our results suggest that delayed institution of ICS therapy in patients with airways obstruction and high reversibility leads to a smaller improvement in airways hyperresponsiveness than earlier introduction. Further prospective studies with longer follow-up are needed to show whether the

damage caused by delayed institution of ICS therapy is permanent or can still be reversed by longer periods of treatment with ICS than the 6 months' duration of this study.

Appendix

The Dutch Chronic Nonspecific Lung Disease (CNSLD) Study Group consists of a steering committee (K.F. Kerrebijn, Ph.H. Quanjer, and H.J. Sluiter†), of members from the departments of pulmonology of the University Hospital of Amsterdam (E.M. Pouw, D.F.M.E. Schoonbrood, C.M. Roos, H.M. Jansen), Groningen (P.L.P. Brand, H.A.M. Kerstjens, A. de Gooijer, D.S. Postma, Th.W. van der Mark, H.J. Sluiter,† G.H. Koëter), Leiden (P.M. de Jong, P.J. Sterk, A.M.J. Wever, J.H. Dijkman), Nijmegen (P.N.R. Dekhuijzen, H. Folgering, C.L.A. van Herwaarden), Rotterdam (S.E. Overbeek, J.M. Bogaard, C. Hilvering), and Utrecht (H.J.J. Mengelers,† S.J. Gans, B. van der Bruggen, J. Kreukniet); from the departments of pediatric pulmonology of Sophia Children's Hospital, Rotterdam (E.E.M. van Essen-Zandvliet, K.F. Kerrebijn), Juliana Children's Hospital, The Hague (E.J. Duiverman, J.M. Kouwenberg, J.E. Prinsen), University Hospital of Groningen (H.J. Waalkens, J. Gerritsen, K. Knol); from the department of allergy of University Hospital, Groningen (J.G.R. de Monchy); from the department of general practice, University of Leiden (A.A. Kaptein, F.W. Dekker); and from the department of physiology, University of Leiden (P.J.F.M. Merkus, Ph.H. Quanjer). Scientific counsel: M.D. Hughes, N.J. Robinson, S.J. Pocock, (London, UK); E.R. Bleecker, D.A. Meyers (Baltimore, Md).

Note: The dagger (†) symbol indicates members of the Dutch CNSLD Study Group, who died before publication of this article.

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