

Effects of nedocromil sodium in steroid-resistant asthma: A randomized controlled trial

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Background: Some patients with asthma respond poorly to corticosteroids and have persistent airway inflammation and daily clinical symptoms. The aim of this study was to investigate the effects of nedocromil sodium (NS), a nonsteroidal antiinflammatory drug, in the treatment of steroid-resistant asthma.

Methods: Steroid-resistant asthma was diagnosed in any patient who demonstrated 20% improvement in FEV₁ after treatment with inhaled salbutamol with failure of FEV₁ to improve by at least 15% after a 2-week trial of prednisolone, 30 mg daily. In a double-blind placebo-controlled trial, the patients received either 4 mg of inhaled NS (n = 13) or placebo (n = 13), 4 times daily for 3 months.

Results: NS but not placebo resulted in a mean increase in FEV₁ of 11.4% after 12 weeks of therapy (p = 0.05) and of 12.4% (p = 0.04) and 15% (0.02) in morning peak expiratory flow after 8 and 12 weeks of treatment, respectively. Changes in FEV₁ at 4 and 8 weeks and in peak expiratory flow at 4 weeks of NS therapy were not significant. NS was also effective in reducing variability of peak expiratory flow (p = 0.02) and use of salbutamol (p = 0.005) and in improving quality of life (p = 0.007) by the trial end. Six of the 12 patients treated with NS who completed the treatment period showed a "good response," defined by a reduction in salbutamol use of more than 50% and an increase in morning peak expiratory flow of more than 20% from baseline; there were no clinical predictors of this response. Two patients were withdrawn from the study because of severe asthma exacerbation (one from each treatment group).

Conclusion: Inhaled NS improved pulmonary function and decreased asthma severity in steroid-resistant asthma, but its effectiveness is not homogeneous and cannot be predicted from baseline clinical data. (*J ALLERGY CLIN IMMUNOL* 1996;97:602-10.)

Key words: Steroid-resistant asthma, asthma treatment, nedocromil sodium

Corticosteroids are the most powerful asthmatic drugs available to us at present. The majority of patients with asthma respond favorably to the administration of these drugs in cases of acute asthma attacks. When corticosteroids are used regularly, they prevent symptoms of asthma in such a way that they are the first line of deep treatment of moderate and severe asthma at present.¹⁻³ An

Abbreviations used

NS: Nedocromil sodium
PEF: Peak expiratory flow
SRA: Steroid-resistant asthma

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undetermined number of patients have asthma that is not sufficiently controlled by corticosteroids, regardless of the way in which the drug is administered or the dose.⁴ This phenomenon has become known as "steroid-resistant asthma" (SRA),⁵ and so far, no satisfactory explanation has been found for it. Patients with SRA have a lower capacity for inhibiting the expression of the neutrophil complement receptors and the proliferation of macrophages and lymphocytes when these cells are cultivated in the presence of corticosteroids.^{6,7} In

addition, many of these patients seem to have resistance of a more general nature to the effects of these drugs, because when they are applied to the skin, the expected paleness caused by the vasoconstrictor effect is reduced.⁸ Other explanations, such as a resistance of genetic origin⁹ or the development of tolerance to the action of corticosteroids, which is of greater concern, have not as yet been discarded.

Corticosteroid-resistant asthma is difficult to treat, because although there is a positive response to the bronchodilators, these drugs used alone are frequently insufficient for the control of the symptoms. Nonsteroidal antiinflammatory drugs, which do not regulate the immunologic cellular response such as cyclosporine or methotrexate, could in theory constitute alternative treatment. Before using these in our therapy and taking into account the considerable side effects of these drugs, we preferred to test the effectiveness of nedocromil sodium (NS), a nonsteroidal antiinflammatory drug with few side effects.¹⁰ This drug, when inhaled, has proved to be useful in the treatment of mild to moderate asthma, and it is known to inhibit the inflammatory process induced by allergic and nonallergic mechanisms; in these processes the T lymphocytes play an important part. Our hypothesis is that NS could also be effective in the treatment of SRA if, as it appears, a persistent inflammatory state that is insensitive to corticoids and partly mediated by activated T cells exists in this form of asthma.

METHODS

Study design

The study was carried out, in patients with stable asthma, as a randomized, double-blind, parallel-group clinical trial; the patients were recruited over a period of 2 years (visit 1). The study comprised two phases. The first phase was a 2-week observation period in which the follow-up capacity of the test protocol in each patient was established and the type and severity of asthma in each of the patients was determined. During this period, all of the patients received 30 mg of prednisolone orally, as well as their usual treatment. If, after the 2-week assessment period, a patient's condition was compatible with the criteria of SRA and he or she demonstrated satisfactory adherence to the protocol, the patient was randomized and introduced into the second phase of the test (treatment period) in which, as well as his or her usual medication, the patient received NS or placebo by means of a manual nebulizer for the next 3 months. Subsequently, this treatment was withdrawn, and the patient continued receiving his or her usual medication for an additional 4 weeks (washout period). The efficacy

of the treatment was assessed according to the data on the daily clinical charts, a questionnaire on the patient's quality of life regarding asthma, and tests related to pulmonary function.

Corticosteroid-resistant asthma

The diagnosis of corticosteroid-resistant asthma was established at the second visit, after 2 weeks of treatment with prednisolone in patients with a stable degree of asthma whose condition was compatible with the following criteria: (1) persistence of asthmatic symptoms; (2) absence of known aggravating or asthma trigger factors after the appropriate assessment of these when they arose; (3) increase in FEV₁ of less than 15% in relation to that of the first visit; and (4) positive bronchodilator test results, assessed as an increase in FEV₁ of more than 20% (plus > 200 ml improvement) after 20 minutes of inhalation of 0.4 mg of salbutamol.

Patients

During visit 1, for the 2-week observation period, nonsmoking adults (>18 years of age) with clinically defined asthma¹¹ who had been treated frequently in our clinic and who had the following characteristics were accepted: (1) moderate or severe degree of asthma³; (2) antecedents in their clinical background of episodes of asthma attack, which had been inadequately controlled by means of inhaled or orally administered corticoids; and (3) basal FEV₁ less than 70% of the predicted value. Patients who regularly used oral prednisolone, those who had previously used NS or cromolyn sodium, and pregnant women or women who were not using a contraceptive method were excluded. The study was approved by the Clinical Trials and Ethics Committee of our medical center, and informed consent was obtained from each of the patients. During visit 2, the patients who were included in the treatment period were those who had SRA (defined above) and who had observed positive adherence to the clinical test, defined as: (1) correct completion of the clinical diary; (2) recording of peak expiratory flow (PEF) morning and night for over 75% of the days, and (3) good completion of the treatment, assessed by means of the difference between the observed cannister weight and the expected weight (this difference should never be less than 20%). Twenty-six subjects (16 women and 10 men) met all of the indicated criteria and were randomized into two groups of 13 subjects each, to be treated with NS or placebo for the next 3 months. The patients were assigned to either of the two groups by means of a randomization program generated by a computer and balanced by two factors: basal FEV₁ and sex. Their clinical characteristics appear in Table I.

Treatment protocol

During the 2-week observation period, each of the patients received 30 mg of prednisolone daily by mouth and inhaled placebo at the rate of 2 puffs, four times

TABLE I. Clinical and lung function data of patients with SRA treated with NS or placebo before randomization

No.	Age (yr)	Sex	Duration of asthma (yr)	FEV ₁ (%pred)	Morning PEF (L/min)	PEF variation (%)	Salbutamol (puffs/day)	IgE (IU/ml)	Atopy (yes/no)	Quality of life (score)	Additional treatment
NS group											
1	35	M	23	47	320	25	6.5	12	No	3.2	Bud, Theo, IB, oral ₂
2	45	F	12	51	210	31	5.7	345	Yes	3.3	Bud, oral ₂
3	53	F	16	63	190	22	4.8	123	No	4.1	Bcl, IB
4	44	M	23	46	310	17	3.9	<10	No	5.2	Theo, IB
5	56	F	7	61	205	26	7.1	65	No	3.1	Bud, oral ₂
6	46	F	11	59	140	16	4.6	1.050	No	5.6	Bud, Theo
7	38	M	16	56	360	19	3.8	10	No	5.7	Bcl, Theo, IB
8	28	F	9	62	220	31	6.7	145	No	2.8	Bud, Theo, oral ₂
9	26	F	18	51	230	26	5.8	122	Yes	3.8	Bcl, IB
10	41	M	22	56	370	16	3.1	<10	No	4.7	Theo, IB
11	52	F	28	42	170	18	4.4	<10	No	4.3	Bud, Theo
12	65	M	16	49	130	20	4.6	25	No	5.1	Bud, oral ₂
13	58	F	25	57	180	16	3.2	78	No	5.6	Bud, Theo, IB
Placebo group											
14	36	F	19	46	207	26	5.6	25	No	3.8	Bud, Theo
15	41	M	14	53	340	28	4.9	234	No	3.4	Bcl, oral ₂
16	50	F	18	55	160	24	4.4	88	No	3.9	Bcl, Theo
17	42	F	20	47	165	23	3.6	456	No	4.9	Theo, IB, oral ₂
18	49	M	26	59	315	15	2.4	<10	No	5.8	Theo
19	59	F	11	63	170	18	2.8	<10	No	5.5	Bud, Theo
20	24	F	5	60	311	28	4.5	670	Yes	4.4	Bud, azelastine
21	30	F	12	55	340	20	4.1	112	Yes	4.9	Bcl, Theo
22	60	M	30	62	290	16	6.8	<10	No	2.8	Bud, Theo, IB, oral ₂
23	28	M	7	62	410	32	6.2	968	No	2.5	Bud, Theo, oral ₂
24	35	F	5	58	260	21	4.4	34	No	3.5	Bcl, IB
25	43	F	16	49	230	22	4.6	45	No	4.6	Bud, oral ₂
26	55	M	24	46	270	18	5.2	16	No	3.7	Bud, Theo, IB

Bud, Inhaled budesonide; *Bcl*, inhaled beclometasone; *Theo*, oral theophylline; *IB*, inhaled ipratropium bromide; *oral₂*, oral β_2 -agonist.

daily. Throughout the test, each patient's usual medication was maintained. Salbutamol, administered through a metered-dose inhaler, was used as rescue medication for all the patients, on demand. During visit 2, the prednisolone dose was reduced by 5 mg per day, and administration was eventually discontinued. During the 3 months after the treatment period, the patients received NS at the rate of 2 puffs, four times daily or inhaled placebo at the same rate. They visited the clinic every 4 weeks to receive an assessment of their asthmatic state, to ensure that the clinical diary was being correctly completed, and to have spirometry carried out. Moreover, throughout the study, a rapid system of consultation with the researchers of the asthma center was available to them, as well as a 24-hour telephone contact system. Asthma exacerbation was declared in situations

in which the patient had to increase the use of β_2 -agonists by 50% for at least 2 consecutive days or when a rapid deterioration in the patient's condition was noted. In the cases in which these episodes arose, the test medication was continued, and the patients were treated individually according to the usual standard medical practice. When the use of corticosteroids was considered advisable, 30 mg of prednisolone per day was administered orally for a period of 7 days; the daily dose was subsequently reduced by 5 mg per day and eventually discontinued. The patients who had to be hospitalized were withdrawn from the study. A patient was considered to have a "good clinical response" (to NS or placebo) if, during the week before the final visit of the treatment period, he or she consumed 50% less salbutamol per day than the amount consumed during the

observation period and his or her morning PEF was 20% greater than that in the observation period.

Clinical and laboratory assessment

During all visits the patients received instructions regarding the way to deal with the daily diary, the possible side effects of the medication were recorded, and a forced spirometry was carried out (Vitalograph; Vitalograph, Inc., Lenexa, Kan.), in which the FEV₁ before and 20 minutes after the administration of 0.4 mg of inhaled salbutamol was measured. In the clinical diary the medication used during the previous 24 hours was recorded every day; and three PEF values, obtained in the morning and on the night before the use of β_2 -agonists or the medication prescribed in the study, were recorded in liters per minute (Mini-Wright peak flow meter; Clement Clarke International, Edinburgh, U.K.). The variability of the PEF was defined as the variation of the morning PEF throughout the last 7 complete days before each visit in accordance with the formula: $PEF_{\text{greatest}} - PEF_{\text{smallest}} \div PEF_{\text{greatest}} \times 100$.

During visit 2, if the patient was included in the active treatment period, a blood sample was taken to perform a standard biochemical analysis, an eosinophil count, and determination of total serum IgE. At this point, the atopic state of the patient was assessed by means of the medical chart and skin prick tests with the following extracts: *Dermatophagoides pteronyssinus*, *D. farinae*, *Artemisia vulgaris*, mixed tree pollen, and mixed grass pollen (Leti Laboratories, Barcelona, Spain). A nonatopic state implied the absence of allergic background and a negative skin test response to all the allergens. During visits 2, 5 (end of treatment period), and 6 (end of washout period) a questionnaire regarding the quality of life especially designed for patients with asthma¹² was administered by a single trained interviewer. It consisted of 32 items referring to symptoms, activities, emotions, and the relation between the asthmatic patient and his or her surroundings. Some of the original questions were modified to adapt them to the needs of our community. The analysis and marking system were not modified, so that each question could be marked from 1 (maximum limitation or discomfort) to 7 (asymptomatic). The total score of the questionnaire was the mean of the sum of all the individual values divided by 32 items.

Statistical study

The primary effectiveness criteria were the morning value of the PEF in liters per minute and the daily use of inhaled salbutamol. The secondary criteria were FEV₁ value, variability of the PEF, value of the questionnaire for quality of life, intake of prednisolone, and number of asthma attacks that occurred during the treatment period. The changes found in FEV₁ between the groups during each visit and the mean morning PEF values, together with the use of salbutamol during the week before each visit in the treatment and washout periods, were compared with their baseline values by means of

TABLE II. Summary of relevant clinical data during the treatment period

	NS group (n = 13)	Placebo group (n = 13)
Good clinical response	6	0
Dropout	1	1
Courses of prednisolone	7 (5 patients)	13 (9 patients)
Emergency visits	2 (2 patients)	4 (3 patients)
Hospital admissions	1	1

Student's *t* test for paired data. The comparison between the groups of these variables was performed by means of Student's *t* test for unpaired data. The values for quality of life were analyzed by means of Wilcoxon's rank-sum test. Values of less than 5% were considered to be statistically significant (two-tailed). All analyses were performed with the SAS statistical package, version 6.04 (SAS Institute, Cary, N.C.).

RESULTS

Twenty-six patients with SRA completed the observation period, fulfilled the inclusion-exclusion criteria during visit 2, and were therefore randomized for the active treatment period. Twenty-three of the 26 subjects completed the treatment and washout periods; two in the placebo group were excluded (weeks 6 and 8 of the treatment period); one dropped out of the study for no apparent reason, and the other was withdrawn because of secondary admission to the hospital after an asthma attack. A patient who received NS was excluded in week 11 as a result of an asthma attack followed by admission to the hospital. The clinical data of all the patients until the end of the testings process were included in the analysis of the results. The clinical characteristics of the patients at the time of initiation of the treatment are shown in Table I. The groups were similar regarding number of patients, age, sex, duration and type of illness, and baseline level of lung function as assessed by FEV₁ as a percentage of the predicted value. The asthmatic state of the patients as evaluated at the time of the randomization by means of the morning PEF, together with its variability, the use of β_2 -agonists, and the quality of life were similar in both groups. None of the patients was an active smoker. The mean compliance rate of the two groups was similar during the observation period. In Table II the most significant data of the clinical evolution are shown. Of the 12 patients who completed the period of NS treatment, six (50%) experienced a "good clinical response"; however, none of the patients who received pla-

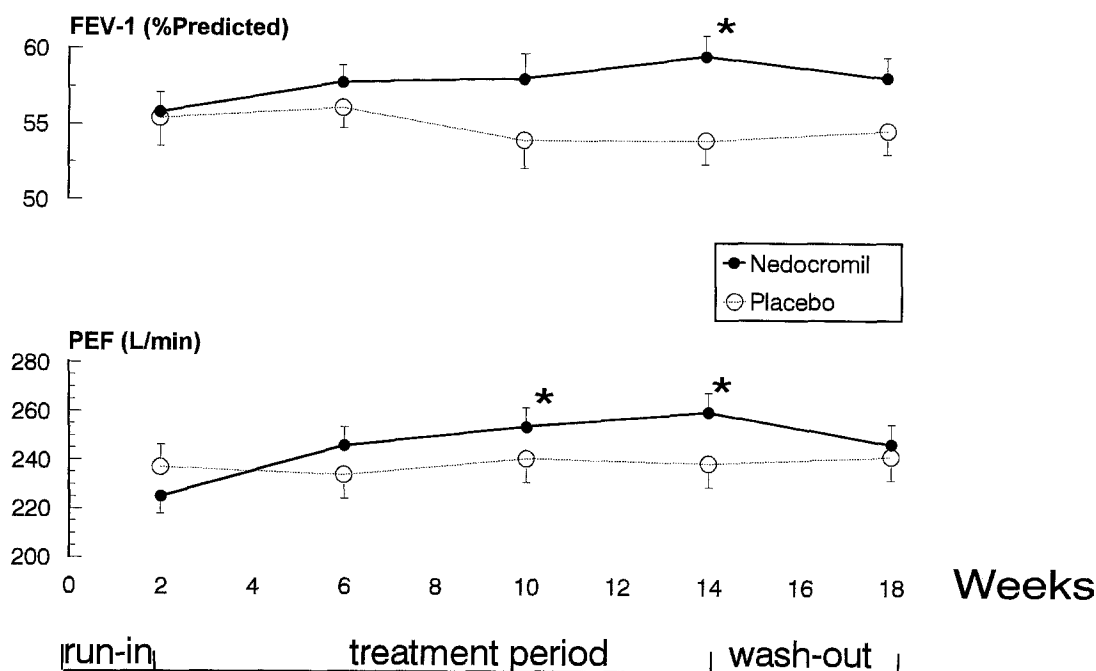


FIG. 1. Mean FEV₁ (percent of predicted value) during each visit (*above*) and mean value of morning PEF in liters per minute during the week before each visit (*below*) for NS (●) and placebo (○). Error bars indicate $\pm$ SEM. * $p < 0.05$ versus baseline.

cebo experienced such a response ($p = 0.01$, Fisher's exact test). Lung function and clinical variables at baseline were not different between the "good responder" and the "nonresponder" subgroups. The number of asthma attacks in which prednisolone courses were used and the frequency with which the patients had to visit the outpatient department because of a worsening of their asthma was lower in the group treated with NS when compared with the group that received placebo. In addition, it is worth pointing out that only one of the patients (no. 2) who received NS and displayed a "good response" to the treatment had an asthma attack during this interim. Side effects in both groups were similar: one patient receiving NS and two receiving placebo reported a transient unpleasant taste, and one patient in each group reported mild coughing; none dropped out of the study.

In Fig. 1 the mean FEV₁ values ($\pm$ SEM) for each visit are shown (percent predicted), together with the values for morning PEF (liters per minute), which appear as the mean for the 7 days with valid measurements before each visit. There was no significant variation between the two parameters in the placebo group throughout the clinical trial. In the NS group changes in FEV₁ were not significant at 4 or 8 weeks but increased

significantly after 12 weeks of treatment (mean change, 11.4%; $p = 0.05$); the morning PEF showed no change at 4 weeks but again also increased from baseline after 8 (mean change, 12.4%; $p = 0.04$) and 12 (mean change, 15%; $p = 0.02$) weeks of treatment. At the end of this period, during the week before visit 5, six of the 12 patients who completed the treatment and had received NS, displayed an increase in morning PEF of over 20% of the value for the week before visit 2 (baseline); four additional patients displayed smaller increases, and in the remaining two subjects, the PEF did not undergo any change. The morning PEF did not increase by more than 3% of the basal value in any patient in the placebo group at the end of the treatment. During the washout period, both the FEV₁ and the morning PEF values were reduced almost to baseline in the group that had received NS.

In parallel fashion to these results, a reduction in the variability of PEF was observed at the 4-week ($p = 0.06$), 8-week ($p = 0.03$), and 12-week ($p = 0.02$) stages of NS treatment when compared with the baseline value. This improvement was maintained until the end of the washout period ($p = 0.03$) (Fig. 2). The use of salbutamol was closely correlated with the variability level of the PEF, both during the run-in period ($r = 0.854$) and at

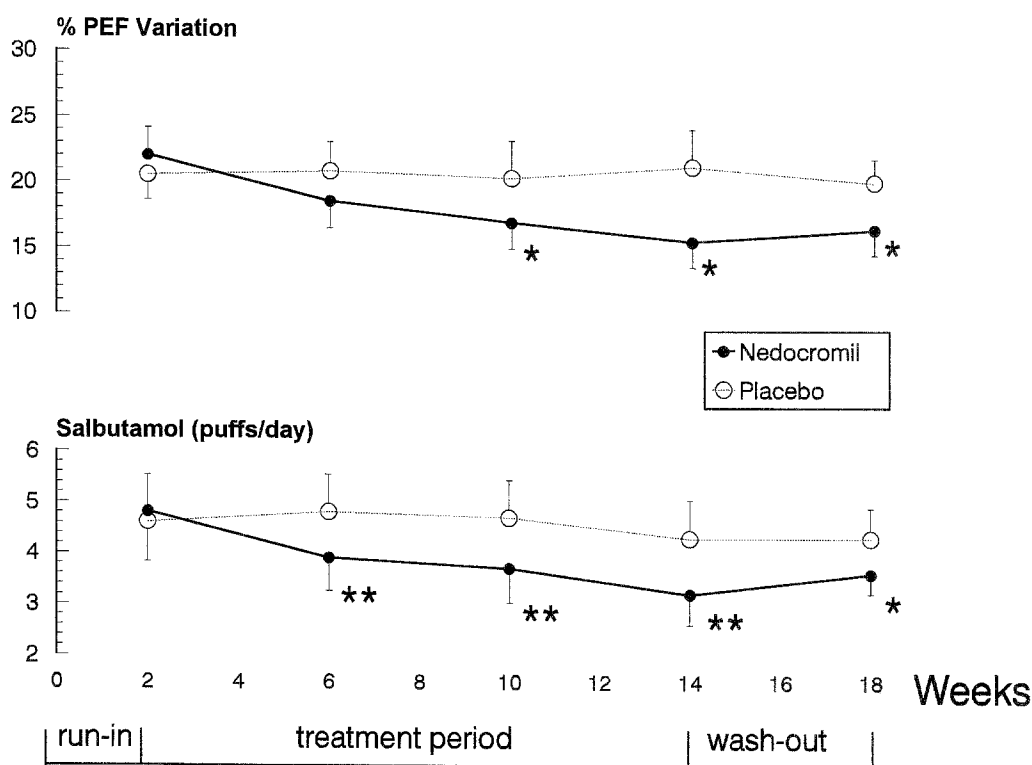


FIG. 2. Mean daytime variations in PEF (above) and mean use of salbutamol (below) during the week before each visit for NS (●) and placebo (○). Error bars indicate $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$ versus baseline.

the end of the treatment ($r = 0.873$) in the patients as a whole. After 4 weeks of treatment with NS, a reduction in the use of salbutamol was observed, from an average of 4.9 puffs per day during the run-in period to 3.9 puffs per day ($p = 0.01$). This difference became even clearer at the 8-week ($p = 0.003$) and 12-week ($p = 0.005$) stages of the treatment. At the end of the washout period, the intake of β_2 -agonists had also decreased in relation to the baseline value ($p = 0.02$). Of the 12 patients who completed the treatment, six demonstrated a reduction of more than 50% in the use of salbutamol by the end of this period, compared with the run-in period. These patients turned out to be the same patients whose morning PEF increased by more than 20% at this time (patients 1, 2, 4, 6, 8, and 10). When the clinical and functional data of these patients were analyzed separately, it was observed that at the 4-week stage of active treatment, morning PEF increased from 245 ± 19 to 288 ± 24 L/min (mean $\pm$ SEM, $p = 0.048$), variability of PEF was reduced from 23.7 ± 1.9 to $15.7\% \pm 1.5\%$ ($p = 0.008$), and inhaled salbutamol intake decreased from 5.1 ± 1.4 to 3.2 ± 1.5 puffs per day ($p = 0.001$). The variability level of

PEF and salbutamol intake during the treatment period was similar to that of the observation period in the group that received placebo. The changes in the variability level of PEF or salbutamol intake were not statistically significant between NS and placebo groups at the end of the treatment.

In Fig. 3 the total value of the Asthma Quality of Life Questionnaire for each patient is shown. Each value represents the mean of the individual values (between 1 and 7) of the 32 items contained in the questionnaire. The baseline values of the two therapeutic groups were similar and displayed great individual variability. On the whole, the quality of life of the group that received NS had increased significantly by the end of the treatment from 4.1 ± 0.2 to 4.6 ± 0.2 ($p = 0.007$). Eleven of the 12 patients who completed the NS treatment improved their quality of life score, and one noted a slight worsening. The six patients who displayed a "good response" to the treatment according to the aforementioned parameters improved their quality of life score by $1.05\% \pm 0.2\%$ (29% when compared with the baseline value). None of the patients who had been treated with placebo im-

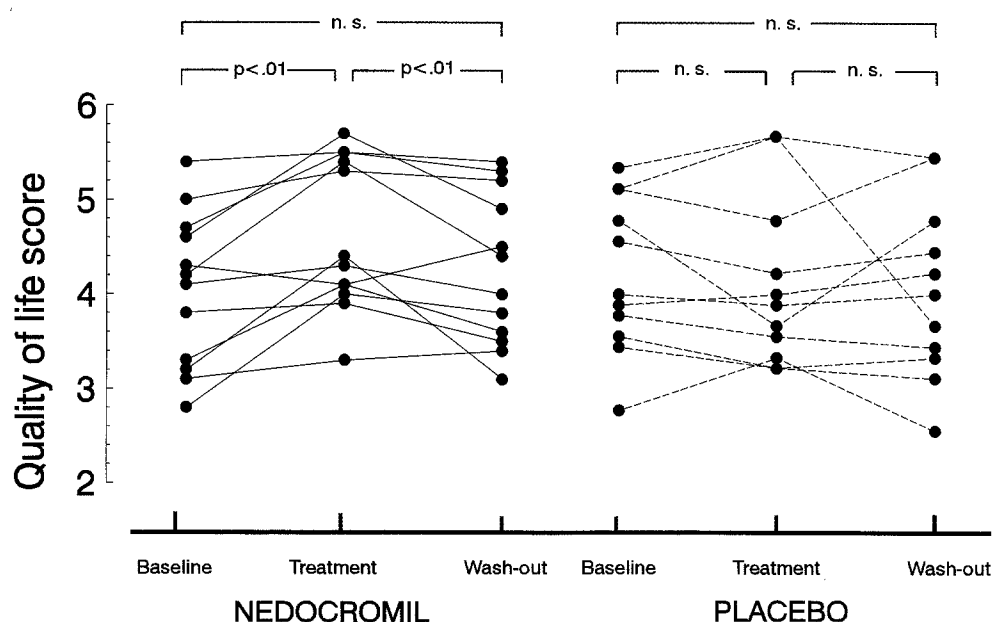


FIG. 3. Effect of NS (*left*) and placebo (*right*) according to a questionnaire on quality of life with asthma for each patient for visit 2 (baseline), visit 5 (end of treatment), and visit 6 (washout).

proved his or her quality of life score by more than 12% at the end of the 12-week treatment period.

DISCUSSION

The patients with SRA who were treated with NS displayed a positive but not homogeneous response to the treatment. The arbitrary criteria outlined in this study as requisites for a "good response" were observed in 50% of the patients who received NS; the remaining half only experienced partial improvements. During the treatment phase, fewer asthma attacks occurred in the patients who had received NS. This reduction was accompanied by moderate increases in lung function and a decrease in the severity of the asthma, which was assessed by the variability level of PEF, the utilization of salbutamol on demand, and the questionnaire on quality of life. When the active treatment was withdrawn and the patients were followed up for another month, no rebound effect was noted; rather, what was of note was the beneficial effect of the NS, especially as far as PEF variability and use of inhaled salbutamol were concerned. Clinical and lung function variables of patients at baseline were not different among responders and nonresponders to inhaled NS, suggesting that the level of response to this therapy in patients with SRA is individual and cannot be predicted before the initiation of treatment. However, 4 weeks after the start of treatment, the patients for whom NS is to be effective can already

be identified. This is the length of time that the drug took to improve the lung function level or the symptoms in other clinical studies of patients with mild or moderate bronchial asthma.^{13, 14} Throughout the study, NS, but not placebo, produced a progressive improvement in lung function level and PEF variability, which reached its peak during the eighth week of treatment. The increase in the morning PEF, a variable that is especially sensitive to fluctuations in asthma stability, and the decrease in the use of β_2 -agonists during the treatment period, when compared with the baseline phase in the patients treated with NS, indicates a decrease in the severity of asthma. Recently, well-controlled clinical trials have also demonstrated the beneficial effects of maintenance treatment with NS on asthma control, particularly in the reduction of the use of bronchodilators in mild to moderately severe asthma.¹⁵⁻¹⁸ In addition, two Canadian and British multicenter double-blind studies, which included patients receiving inhaled corticosteroids whose asthma was poorly controlled showed that NS added to the treatment provided clinical benefit.^{19, 20} In this study, given the initial degree of severity of the illness of our patients, we did not believe it was suitable to modify their usual anti-asthma treatment. However, the reduced need for additional courses of prednisolone in the group that received NS supports its stabilizing effect in asthma.

The airflow limitation in patients with SRA is

severe and stable in time, as demonstrated by the absence of functional changes in the group treated with placebo. In the absence of morphologic studies of the airways, the bronchial irreversibility and the insensitivity of airway limitation to corticoids in patients with SRA does not seem to conform to structural anatomic alterations, given the positive response to β_2 -agonists and antiinflammatory drugs, such as cyclosporine²¹ or methotrexate²² in some patients. The useful effect of these drugs in SRA also indicates that in this type of asthma there is a persistent inflammation of the airways, in spite of corticoid treatment. The cellular changes implied in this type of inflammation are probably similar to those of patients with corticosteroid-sensitive asthma, bearing in mind the action mechanism of the methotrexate and the cyclosporine. In the pathogenesis of SRA, T lymphocytes and their products play an important role, in such a way that glucocorticoids do not inhibit the induced proliferation of T lymphocytes or the production of lymphokines.²³ This might explain the effectiveness of cyclosporine in severe asthma, because this drug acts mainly by inhibiting the activation of T lymphocytes.²⁴ Other authors have described additional effects in the cellular response to corticoids in SRA. Pozansky et al.²⁵ found a lack of inhibition by glucocorticoids of the proliferation of activated monocytes; Alvarez et al.²⁶ confirmed these findings and also found that a greater and unbraked proliferation of T lymphocytes existed when the mononuclear cells were stimulated by phytohemagglutinin and incubated in the presence of corticosteroids. As a consequence, an increase in DNA synthesis took place, which is an essential step in the production of proinflammatory proteins. In the same study the administration of troleandomycin, a macrolide with immunoregulatory properties, reverted the increase of synthesis of the DNA in vitro and produced a clinical improvement in four of the five patients with SRA to whom it was administered. Lastly, Lane et al.²⁷ discovered that in patients with SRA steroids have a selective capacity for inhibiting the 3 kd neutrophil priming activity derived from the monocytes, which in turn stimulates the production of leukotrienes by neutrophils. All these data suggest that the lack of antiinflammatory action of corticosteroids in patients with SRA contributes to maintaining an inflammatory state in the airways and that other immunoregulators could be clinically useful. Our initial hypothesis, that the presumed effectiveness of NS in SRA should be at least partly justified by its blocking effect on the lymphocytic activity, has

recently been confirmed in a study by Mekori et al.²⁸ These authors, using murine lymphocytes, found that NS inhibited the mitogen- or antigen-induced proliferative responses of these cells and also interfered with the mitogen-induced IL-2 and tumor necrosis factor production by T cells. The clinical response to NS in our patients has nonetheless been unpredictable, but it does encourage the continued use of trials with non-steroidal antiinflammatory drugs for patients with asthma when there is a growing concern regarding the overuse of β_2 -agonists and the side effects of corticosteroids.²⁹

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