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Response to corticosteroids in chronic airflow obstruction: relationship to emphysema and airways collapse

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ABSTRACT: We have studied the relationship between emphysema and airways collapse, and response to corticosteroids in patients with chronic airflow obstruction. One hundred and seven patients completed a placebo-controlled trial comparing 2 wks treatment with oral prednisolone 40 mg·day^{-1} to inhaled beclomethasone dipropionate 500 μg *t.d.s.* Response to corticosteroids was defined on the basis of changes in forced expiratory volume in one second (FEV_1), and/or forced vital capacity (FVC), and/or mean peak expiratory flow (PEF) after treatment.

Patients were categorized as those with physiologically defined emphysema (carbon monoxide transfer coefficient (Kco) <70% predicted and total lung capacity >120% predicted), and those with pressure dependent airways collapse on the flow-volume loop (ratio of inspiratory to expiratory flow at 50% vital capacity [$I:E_{50}$] >10).

The response to placebo showed a significant order effect, probably due to a carry-over effect of active treatment of at least 3 wks. Hence, the efficacy of active treatment over placebo in the subgroups defined was assessed by analysis of data generated from the first treatment phase of the trial. The presence or absence of physiologically defined emphysema did not affect the response to oral prednisolone. Inhaled beclomethasone dipropionate, however, was less effective in the emphysema group. Pressure dependent airways collapse did not affect the response to either prednisolone or beclomethasone. However, when data from all three treatment phases were analysed there was no significant difference in the response to either drug in any of the subgroups defined.

These results indicate that a response to oral prednisolone occurs as frequently in patients with physiological features of emphysema as in those without, and that patients with emphysema should, therefore, not be excluded from a therapeutic trial of corticosteroids.

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Chronic airflow obstruction in adults can sometimes respond to corticosteroids with subsequent partial relief of the patient's breathlessness when response is measured over two to four weeks. Because of the large number of potential candidates for a trial of corticosteroids, the time taken in assessing any change, and the relatively poor return in terms of response [1–3], patients whom the clinician believes to be unlikely to respond are often denied a trial. Patients with emphysema are often excluded, as it is not apparent how the airways obstruction associated with emphysema, which is pathologically irreversible, could respond to corticosteroids.

This study reports further analysis of data collected as part of a trial comparing oral and inhaled corticosteroids previously reported [3]. The aim was to investigate whether patients with physiologically defined chronic airflow obstruction and emphysema showed a different response to corticosteroids compared with those who did not have emphysema. We also investigated whether pressure dependent airways collapse, a feature previously associated with emphysema [4], mitigated against a steroid response. It seemed unlikely that expiratory airways collapse due to loss of airway support in emphysema would be influenced by corticosteroids.

Methods

Subjects

Out-patients with adult onset chronic airflow obstruction of at least 5 yrs duration and forced expiratory volume in one second (FEV_1) <70% predicted were

recruited to the trial. Patients were excluded if there was a clinical diagnosis of asthma. Asthma was likely if there had been respiratory symptoms in childhood, if there was variability in symptoms apart from with infections, if acute attacks of wheezing and breathlessness occurred, and if there was a deterioration following specific allergen exposure. A lack of a "fixed" element to the airflow obstruction following bronchodilator also suggested asthma as the diagnosis. The presence of some airflow reversibility to inhaled bronchodilators was deliberately not chosen as an exclusion criteria. No patient had received oral or inhaled corticosteroids in the preceding six months. All patients gave verbal informed consent and the study was approved by the local Ethical Committee.

Study design

The patients underwent a double-blind, double-dummy, randomized, crossover trial of oral prednisolone 40 mg·day^{-1} and a placebo inhaler, inhaled beclomethasone dipropionate 500 μg *t.d.s.* and placebo tablets, and both preparations as placebo. Each treatment was given for two weeks with a two week wash-out phase in between. All of the treatment phases looked identical.

Measurements

Spirometry was performed on three separate days and lung volumes were measured once prior to the administration of any drugs. Spirometry was repeated on the last day of each treatment phase. The patients were asked to abstain from inhaled bronchodilators for the 6 h preceding any attendance and all visits were made at the same time of day. The FEV_1 and forced vital capacity (FVC) were measured on a dry bellows spirometer (Vitalograph). On each occasion the mean of three technically satisfactory attempts within the smaller of 10% or 100 ml was recorded. The baseline FEV_1 or FVC was the highest mean measurement before treatment was started.

Flow-volume loops were recorded on a high speed X-Y recorder (Bryans 26700) linked to a P.K. Morgan flow volume module attached to a rolling seal spirometer. The flow rates were measured directly from the loop using a ruler. The mean of three satisfactory attempts was used for analysis.

Total lung capacity (TLC) and residual volume (RV) were measured by helium dilution. The test was continued until the helium concentration was stable, to a maximum time of 20 min. Transfer factor for carbon monoxide (TLco) and the transfer coefficient for carbon monoxide (Kco), were derived from the mean of two single breath estimations. The full details of the trial are given elsewhere [3].

Predicted values for lung function variables are from the European Community for Coal and Steel (ECCS) predictive equations [5]. Reversibility of FEV_1 to salbutamol is presented as the change expressed as a percentage of the predicted value [6].

Analysis

Physiological emphysema was defined as 1) Kco <70% predicted; and 2) total lung capacity of >120% predicted. The ratio of inspiratory to expiratory flow at 50% of the vital capacity ($I:E_{50}$) was measured from the flow volume loop. An "expiratory collapse" pattern was identified where the ratio of inspiratory to expiratory ratio at 50% of vital capacity was >10 (fig. 1).

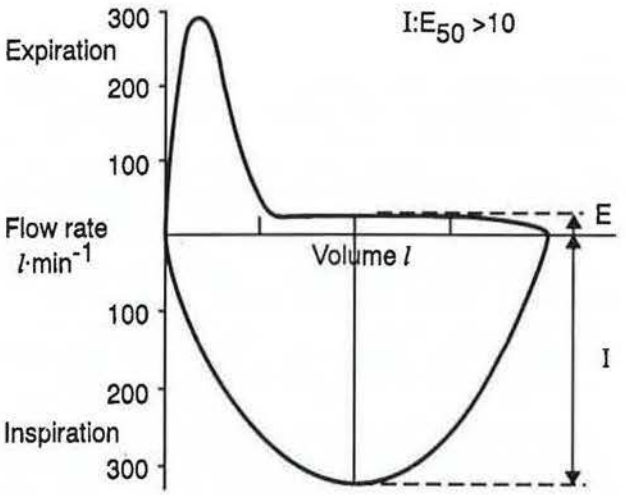

Fig. 1. – A flow-volume loop showing the parameters used to calculate the $I:E_{50}$. E: expiratory flow at 50% vital capacity; I: inspiratory flow at 50% vital capacity.

The initial analysis showed a significant placebo order effect, that is a response to placebo treatment was more likely to occur if the placebo was given after an active treatment [3], suggesting a carry-over effect of active treatment in excess of three weeks. No significant order effect was seen with either active treatment. Because of this placebo order effect, response to treatment was defined with respect to baseline values, obtained before the administration of any trial medication.

The efficacy of active treatment over placebo in the defined subgroups was, therefore, assessed by a parallel group analysis of the first treatment phase data. Response rates to the two active treatments in each subgroup was assessed by analysis of the data from all phases of the trial as the order effect was only significant for placebo response.

A full response to active treatment was defined as ≥20% improvement in FEV_1, FVC or mean peak flow during the second week of treatment when compared to baseline. A response of ≥10% in any two parameters or ≥15% in any one parameter was initially defined as a partial response, but for this analysis partial and full responses are combined.

Statistics

The comparisons of baseline data were made by unpaired Student's t-tests. Appropriate confidence intervals for the differences in response rates between the different subgroups and their significance were calculated as suggested by ARMITAGE [7]. $I:E_{50}$ ratios were not normally distributed and a logarithmic transformation was used in the analysis.

Results

One hundred and twenty seven patients entered the study and 107 (25 female) completed it. Eleven patients failed to attend subsequent visits, six had an infective exacerbation of their disease, two developed concurrent medical problems whilst taking prednisolone, and one patient died of an unrelated cause during the baseline period. The mean age of the patients was 63 (SEM 0.8) yrs, mean absolute FEV_1 1.19 (0.47) *l*, or 44 (1.6) as percentage predicted FEV_1. The mean Kco was 1.13 (0.05) $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot l^{-1}$ or 78 (31.7) as percentage predicted.

Thirty five patients satisfied the criteria for physiological emphysema (table 1). Patients with physiological emphysema had a similar impairment in FEV_1 but higher levels of FVC. All were current or ex-smokers and had smoked more than those without emphysema.

Table 1. – Baseline characteristics of the two groups with and without physiological emphysema, (mean±SEM)

	With emphysema	Without emphysema
n M/F	35/6	72/19
Age yrs	63±1.4	63±1.1
FEV_1 *l*	1.17±0.09	1.20±0.05
FEV_1 % pred	42±3.1	46±1.9
FVC *l*	2.92±0.14	2.52±0.08*
FVC % pred	86±3.7	77±2*
Reversibility to 10 mg salbutamol as % pred #	6.1±0.9	7.7±0.7
Smoking status		
curent smokers	17	24
ex-smokers	18	36
lifelong nonsmokers	0	12*
Cigarette consumption pack-yrs	46±5	34±3*
$I:E_{50}$ ratio as geometric mean (range)	6.0 (1–26)	5.31 (1–22)

#: % pred = (postbronchodilator FEV_1 - prebronchodilator FEV_1)/predicted FEV_1 × 100; *: $p<0.05$; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $I:E_{50}$: ratio of inspiratory to expiratory flow at 50% of vital capacity.

Twenty two patients had an expiratory collapse pattern on their flow-volume loop (table 2). Patients with pressure dependent airways collapse were of similar age to those without but had smoked slightly more and had significantly lower values for FEV_1. Only six patients fulfilled both the criteria for physiological emphysema and pressure dependent airways collapse. The correlation in all 107 patients between $\log_e I:E_{50}$ and Kco was poor (r=-0.19; NS).

Table 2. – Baseline characteristics of the two groups with and without airways collapse ($I:E_{50}$ >10) (mean±SEM)

	$I:E_{50}$ >10	$I:E_{50}$ <10
n M/F	22/2	85/23
Age yrs	64±1.9	63±1
FEV_1 *l*	1.02±0.06	1.23±0.05*
FEV_1 % pred	36±2.2	46±1.9*
FVC *l*	2.8±0.15	2.61±0.09
FVC % pred	80±3.5	79±2.2
Reversibility to 10 mg salbutamol as % pred	6.0±1.5	7.5±0.6
Kco $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot l^{-1}$	1.11±0.09	1.13±0.05
Kco % pred	74±6.5	79±3.5
Maximum inspiratory flow $l \cdot min^{-1}$	274±14	185±8*
Smoking status		
current smokers	7	34
ex-smokers	15	39
lifelong nonsmokers	0	12
Cigarette consumption pack-yrs	44±4.3	37±3.1

*: $p<0.05$; Kco: carbon monoxide transfer coefficient. For further definitions see legend to table 1.

Analysis of the first phase data to compare placebo with active treatment in the subgroups

Thirty five patients received placebo treatment as the first of the three crossover treatments, 34 patients inhaled beclomethasone alone, and the remaining 38 patients oral prednisolone (table 3). The patients in each treatment group did not differ in terms of baseline physiological characteristics [3].

The numbers of patients showing a response to inhaled beclomethasone or oral prednisolone was significantly greater than that seen to placebo in the subgroup of patients without physiological emphysema. In the group with physiological emphysema, however, only prednisolone showed a response rate greater than that to placebo. No patients in this subgroup showed a response to inhaled beclomethasone.

In the subgroup without pressure dependent airways collapse the response to oral prednisolone and inhaled beclomethasone was greater than that seen after placebo, but only statistically significant for prednisolone. In the 22 patients with pressure dependent airways collapse similar effects of both active treatments were seen, but statistical analysis produced wide confidence limits for the difference from placebo response rate because of the small total number of patients in each group. The difference (95% confidence limits) to placebo response rate for beclomethasone was 43% (88 to -2), for prednisolone 48% (91 to 6). If both active treatments are combined the response rate to active treatment is significantly greater than to placebo (difference 46% (82 to 10); $p<0.05$).

Table 3. – The number of responders seen to each treatment in the defined subgroups in the first phase of the trial

Physiological emphysema groups		
	Present	Absent
Placebo	1/11	3/24
Prednisolone	7/14*	10/24*
BDP	0/10	12/24*
$I:E_{50}$ groups		
	>10	<10
Placebo	1/7	3/28
Prednisolone	5/8	12/30*
BDP	4/7	8/27

*: $p<0.05$ for comparison of response rate to placebo within each subgroup. BDP: beclomethasone dipropionate; $I:E_{50}$: ratio of inspiratory to expiratory flow at 50% of vital capacity.

Analysis of data from all three phases of the trial to compare corticosteroid responsiveness between subgroups

The data from all three phases of the trial has been used to compare response to each active treatment in the subgroups. No significant difference was seen between response to oral prednisolone or inhaled beclomethasone in the two pairs of subgroups defined.

A response to oral prednisolone was seen in 31 out of 72 (43%) of patients who had no evidence of physiological emphysema, and in 13 out of 35 (37%) of patients with emphysema. A response to inhaled beclomethasone occurred in 25 out of 72 (35%) of patients without physiological emphysema as defined, compared to 11 out of 35 (31%) of patients with emphysema.

In patients defined on the basis of the presence or absence of an expiratory collapse pattern on the flow-volume loop, a response to oral prednisolone was seen in 32 out of 85 (38%) of those without collapse, compared to 12 out of 22 (54%) of those with. Response to inhaled beclomethasone was similar in those with expiratory collapse, 9 out of 22 (41%), and in those without, 27 out of 85 (32%).

Discussion

We were concerned that patients with chronic airflow obstruction and emphysema are denied the possible beneficial effects of corticosteroid treatment. Hence, one of the aims of the main study was to determine whether emphysema, diagnosed in life, affected the physiological response to corticosteroids. The interpretation of our data is complicated by the placebo order effect we found on the initial analysis [3, 8], and the need to perform a parallel group analysis of the first phase data to overcome this problem when comparing active treatments to placebo. Our data do show an effect of both oral prednisolone and inhaled beclomethasone in the 107 patient group which is significantly greater than that seen after placebo [3]. In the subgroups we defined, however, the smaller numbers of patients analysed produce wide confidence limits for the difference between active treatment and placebo, and some comparisons in our analysis may lack enough statistical power to detect effects of active treatment which do exist.

Our data indicate that oral prednisolone is effective in producing physiological response in patients irrespective of the presence of physiological emphysema or pressure dependent airways collapse. Inhaled beclomethasone appears effective in patients with pressure dependent airways collapse, but we found no responses to this drug in the ten patients with physiological emphysema who received this treatment as the first phase treatment. This apparent lack of response may reflect a failure of the drug to reach the airways adequately, secondary to alterations in inspiratory flow and hence aerosol deposition. Alternatively, it may reflect the small number of patients in this subgroup. For, when the data from all three phases of the trial are analysed, the number of responses seen to inhaled beclomethasone is not different between the two physiological emphysema groups.

Strictly, emphysema is defined pathologically as dilatation of the airspaces distal to the terminal bronchiole with destruction of alveolar septa. Faced with a living patient, however, this definition is of little practical use. We chose a definition of physiological emphysema based upon published evidence from clinicopathological studies, which have utilized antemortem lung function and graded emphysema histologically on postmortem or postoperative specimens [9–11]. These studies show a moderately strong correlation between measures of carbon monoxide gas transfer and histological emphysema, a correlation which is stronger when techniques which detect less severe emphysema are used [9]. In addition we included a measure of hyperinflation as suggested by WEST *et al.* [11] to exclude any patients with mixed fibrotic and obstructive lung processes.

The fact that patients with emphysema show responses to treatment in parameters which reflect

airway obstruction may indicate that at least in these responsive patients the major cause of the airflow obstruction resides in the airway wall. It seems unlikely that an improvement in airflow could be obtained if the main determinant of the airflow obstruction seen was lack of airway support due to peribronchiolar emphysema [12], which should be irreversible. The likeliest mode of action of corticosteroids is as an anti-inflammatory agent, as is postulated in asthma. The results of the reversibility tests indicate that the majority of the patients studied had non-asthmatic airflow obstruction [6], so the results may indicate an effect of corticosteroids on the neutrophilic bronchial wall inflammation seen in this group of patients [13]. If a direct effect of corticosteroids on airway inflammation is not the explanation, then one must postulate that corticosteroids alter the compliance of the emphysematous alveoli by mechanisms which are not clear.

Pressure dependent airways collapse may also result from loss of alveolar support to the small airways [12]. DENISON *et al.* [4] suggest that a ratio of inspiratory to expiratory flow at 50% of the vital capacity of >10, is associated with emphysema. Our results however showed a poor correlation between this measure and the KCO, suggesting other factors play a major part in determining airways collapse. The presence of pressure dependent airways collapse did not influence corticosteroid responsiveness in our patients.

There have been a number of other studies of corticosteroid responsiveness in chronic obstructive airways disease (COAD), however, in only a minority has emphysema been defined adequately in the patients studied. Two studies have used similar physiological definitions to ours [14, 15]. BLAIR and LIGHT [14] found no correlation between initial gas transfer and spirometric response to prednisolone 32 mg·day^{-1} or 64 mg on alternate days in 44 patients with COAD, although some patients with reduced gas transfer did show improvement. BEEREL and VANCE [15] showed no mean improvement in a group of 23 patients treated with prednisolone 30 mg·day^{-1} for 8 wks, although gas transfer did improve in this study and in that of O'REILLY *et al.* [16]. In other studies corticosteroid responses were seen in 2 of 10, 0 of 7 and 0 of 7 patients with physiological emphysema [17–19], although the dose of corticosteroid used in the second trial was relatively low (betamethasone 1.8 mg·day^{-1}, equivalent to 16 mg prednisolone).

Our study suggests that patients with physiological features of emphysema respond to oral prednisolone as well as patients without these features. Although a response to inhaled beclomethasone may not be as common, the presence of features of emphysema should not prevent physicians from offering a trial of corticosteroids when indicated in this group of patients.

References

1. Eliasson O, Hoffman J, Trueb D, Frederick D, McCormick JR. – Corticosteroids in COPD. *Chest*, 1986, 89, 484–490.
2. Stokes TC, Shayler JM, O'Reilly JF, Harrison BDW. – Assessment of steroid responsiveness in patients with chronic airflow obstruction. *Lancet*, 1982, 2, 345–348.
3. Weir DC, Gove RI, Robertson AS, Burge PS. – Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone with inhaled beclomethasone dipropionate. *Thorax*, 1988, 45, 112–117.
4. Dennison DM, Waller JF, Turton CWG, Sopwith T. – Does the lung work? 5. Breathing in and breathing out. *Br J Dis Chest*, 1982, 76, 237–252.
5. Quanjer P, ed. – Standardised lung function testing. *Bull Eur Physiopathol Respir*, 1983, 19 (Suppl. 5), 1–95.
6. Meslier N, Racineux JL, Six P, Lockhart A. – Diagnostic value of reversibility of chronic airways obstruction to separate asthma from chronic bronchitis: a statistical approach. *Eur Respir J*, 1989, 2, 497–505.
7. Armitage P. – *In:* Statistical methods in medical research. Blackwell Scientific Publications, Oxford, 1971, pp. 126–128.
8. Weir DC, Robertson AS, Gove I, Burge PS. – Time course of response to oral and inhaled corticosteroids in non-asthmatic chronic airflow obstruction. *Thorax*, 1990, 45, 117–120.
9. Gould GA, MacNee W, McLean A, Warren PM, Redpath A, Best JJK, Lamb D, Flenley DC. – CT measurements of lung density in life can quantitate distal airspace enlargement, an essential defining feature of human emphysema. *Am Rev Respir Dis*, 1988, 137, 380–392.
10. Bergin C, Muller N, Nichols DM, Lillington G, Hogg JC, Mullen B, Grymaloski MR, Osborne S, Pare PD. – The diagnosis of emphysema. A computed tomographic-pathologic correlation. *Am Rev Respir Dis*, 1986, 133, 541–546.
11. West WW, Nagai A, Hodgkin JE, Thurlbeck WM. – The National Institutes of Health Intermittent Positive Pressure Breathing Trial - Pathology studies. The diagnosis of emphysema. *Am Rev Respir Dis*, 1987, 135, 123–129.
12. McLean A, Lamb D, Gould G, Warren P, Flenley DC. – Morphometric factors associated with airflow limitation in early COAD. *Thorax*, 1987, 42, 210.
13. Rennard SI, Daughton D, Fujita J, Oehlerking MB, Dobson JR, Stahl MG, Robbins RB, Thompson AB. – Short-term smoking reduction is associated with reduction in measures of lower respiratory tract inflammation in heavy smokers. *Eur Respir J*, 1991, 3, 752–759.
14. Blair GP, Light RW. – Treatment of chronic obstructive pulmonary disease with corticosteroids: comparison of daily *vs* alternate day therapy. *Chest*, 1984, 86, 524–528.
15. Beerel FR, Vance JW. – Prednisolone treatment of stable pulmonary emphysema. *Am Rev Respir Dis*, 1971, 104, 264–266.
16. O'Reilly JF, Shaylor JM, Fromings KM, Harrison BDW. – The use of the 12 minute walking test in assessing the effect of oral steroid therapy in patients with chronic airways obstruction. *Br J Dis Chest*, 1982, 76, 374–382.
17. Beerel F, Jick H, Tyler JM. – A controlled study of the effects of prednisone on airflow obstruction in severe pulmonary emphysema. *New Engl J Med*, 1963, 268, 226–230.
18. Morgan WKC, Rusche E. – A controlled trial of the effects of steroids in obstructive airways disease. *Ann Intern Med*, 1964, 61, 248–254.
19. Pecora LJ, Zoss AR, Baum GL *et al.* – A study of the physiologic effects of intravenous methylprednisolone in chronic pulmonary emphysema. *Am Rev Respir Dis*, 1964, 89, 528–531.

Réponse aux corticostéroïdes dans l'obstruction chronique du débit aérien: relations avec l'emphysème et le collapsus des voies aériennes. D.C. Weir, R.I. Gove, A.S. Robertson, P. Sherwood Burge.

RÉSUMÉ: Nous avons étudié les relations entre l'emphysème et le collapsus des voies aériennes d'une part, et la réponse aux corticostéroïdes d'autre part, chez les patients atteints d'obstruction chronique du débit aérien. Un essai contrôlé par placebo a été conduit chez 107 patients, avec comparaison de deux semaines de traitement au moyen de prednisolone orale à raison de 40 mg par jour, et de 500 mcg de beclomethasone en inhalation 3 fois par jour. Une réponse aux corticostéroïdes a été définie sur la base de modifications du VEMS, et/ou de la capacité vitale forcée, et/ou du débit expiratoire de pointe moyen (PEF) après traitement.

Les patients ont été classés, d'une part comme emphysème défini physiologiquement (Kco <70% et capacité pulmonaire totale >120% des valeurs prédites), et d'autre part comme présentant un collapsus des voies aériennes lié à la pression sur la courbe débit volume (ratio du débit inspiratoire au débit expiratoire à 50% de la capacité vitale [$I:E_{50}$] >10).

La réponse au placebo a montré un effet d'ordre significatif, probablement dû à un effet rémanent du traitement actif pendant au moins 3 semaines. Dès lors, l'efficacité du traitement actif par rapport au placebo dans les sous-groupes définis a été appréciée par l'analyse de données provenant de la première phase de traitement de l'essai. La présence ou l'absence d'emphysème défini physiologiquement n'a pas d'effet sur la réponse à la prednisolone orale. Toutefois, le dipropionate de beclomethasone en inhalation s'avère moins efficace dans le groupe emphysémateux. L'existence d'un collapsus des voies aériennes lié à la pression n'affecte la réponse, ni à la prednisolone, ni à la beclomethasone. Toutefois, quand les données provenant des trois phases de traitement sont analysées, l'on ne trouve pas de différence significative dans la réponse à aucune des deux drogues dans aucun des sous-groupes définis.

Ces résultats indiquent qu'une réponse à la prednisolone orale se produit aussi fréquemment chez les patients ayant les caractéristiques physiologiques de l'emphysème que chez ceux qui en sont dépourvus, et que les patients atteints d'emphysème ne devraient pas être récusés pour un essai thérapeutique aux corticostéroïdes.

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