EFFECT OF SYSTEMIC GLUCOCORTICOIDS ON EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background and Methods Although their clinical efficacy is unclear and they may cause serious adverse effects, systemic glucocorticoids are a standard treatment for patients hospitalized with exacerbations of chronic obstructive pulmonary disease (COPD). We conducted a double-blind, randomized trial of systemic glucocorticoids (given for two or eight weeks) or placebo, in addition to other therapies, for exacerbations of COPD. Most other care was standardized over the six-month period of follow-up. The primary end point was treatment failure, defined as death from any cause or the need for intubation and mechanical ventilation, readmission to the hospital for COPD, or intensification of drug therapy.

Results Of 1840 potential study participants at 25 Veterans Affairs medical centers, 271 were eligible for participation and were enrolled; 80 received an eight-week course of glucocorticoid therapy, 80 received a two-week course, and 111 received placebo. About half the potential participants were ineligible because they had received systemic glucocorticoids in the previous 30 days. Rates of treatment failure were significantly higher in the placebo group than in the two glucocorticoid groups combined at 30 days (33 percent vs. 23 percent, P=0.04) and at 90 days (48 percent vs. 37 percent, P=0.04). Systemic glucocorticoids (in both groups combined) were associated with a shorter initial hospital stay (8.5 days, vs. 9.7 days for placebo; P=0.03) and with a forced expiratory volume in one second that was about 0.10 liter higher than that in the placebo group by the first day after enrollment. Significant treatment benefits were no longer evident at six months. The eight-week regimen of therapy was not superior to the two-week regimen. The patients who received glucocorticoid therapy were more likely to have hyperglycemia requiring therapy than those who received placebo (15 percent vs. 4 percent, P=0.002).

Conclusions Treatment with systemic glucocorticoids results in moderate improvement in clinical outcomes among patients hospitalized for exacerbations of COPD. The maximal benefit is obtained during the first two weeks of therapy. Hyperglycemia of sufficient severity to warrant treatment is the most frequent complication. (N Engl J Med 1999;340:1941-7.)

PATIENTS with chronic obstructive pulmonary disease (COPD) frequently have exacerbations that require hospitalization. Hospital treatment for this common condition is associated with high costs and relatively poor outcomes.[1] In addition to antibiotics, oxygen, and bronchodilators, most hospitalized patients receive systemic glucocorticoids. Less severely ill patients often receive oral glucocorticoids as outpatients.

Systemic glucocorticoids improve outcomes in patients with acute asthma,[2] but their clinical efficacy in the treatment of COPD is less clear. Two small trials suggested that several days of therapy with systemic glucocorticoids improved the forced expiratory volume in one second (FEV_1) during exacerbations of COPD.[3,4] Another trial found that a single dose of methylprednisolone did not improve spirometric results over the succeeding five hours.[5] None of these trials were explicitly designed to evaluate clinical outcomes. The role of systemic glucocorticoids in patients with stable COPD is similarly unclear.[6]

Adverse effects of the short-term administration of systemic glucocorticoids include secondary infections, hyperglycemia, and a range of mood and behavioral changes.[7] Long-term therapy may cause osteoporosis, cataracts, hypertension, myopathy, and adrenal insufficiency.

We conducted a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy of systemic glucocorticoids for exacerbations of COPD. The principal objective was to determine rates of treatment failure. A secondary goal was to determine the optimal duration of treatment.

METHODS

The Human Rights Committee of the Veterans Affairs Cooperative Studies Program and the institutional review boards of the participating medical centers approved this study. All patients gave written informed consent.

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*Other investigators who participated in the study are listed in the Appendix.

Study Design

We designed this study to assess the equivalence of two approaches to the treatment of COPD.[8,9] Systemic glucocorticoids are the standard therapy for hospitalized patients with COPD, even though they have adverse effects. Therefore, the withholding of glucocorticoids may be viewed as an experimental intervention associated with no glucocorticoid-related complications. The planning committee settled on a 7.5 percent absolute difference in the rate of treatment failure as the clinically meaningful upper limit. In other words, withholding glucocorticoids would be considered the preferred treatment if the results showed a difference in the failure rate (the rate with placebo minus the rate with active treatment) of 7.5 percent or less. The secondary objective was to assess the equivalence of two different periods of therapy (two and eight weeks). The follow-up period lasted for six months from the time of enrollment. A detailed description of the rationale for the study, its design, the protocol, and the planned analyses is provided elsewhere.[10]

Study Population

All patients admitted to participating Veterans Affairs medical centers for exacerbations of COPD were potential subjects. The principal inclusion criteria were a clinical diagnosis of exacerbation of COPD, an age of 50 years or more, a history of 30 pack-years or more of cigarette smoking, and either an FEV_1 of 1.50 liters or less or an inability to undergo spirometry because of dyspnea. The principal exclusion criteria were a diagnosis of asthma, use of systemic glucocorticoids within the preceding 30 days, coexisting medical conditions that made survival for at least 1 year unlikely, and inability to give informed consent. We obtained base-line data on respiratory disease and other pertinent aspects of the medical history by means of a questionnaire.[11]

Treatments

We randomly assigned patients within 12 hours after presentation to one of three treatment groups. The first group received eight weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Kalamazoo, Mich.) (given in a dose of 125 mg every 6 hours for 72 hours) followed by once-daily oral prednisone (60 mg on study days 4 through 7, 40 mg on days 8 through 11, 20 mg on days 12 through 43, 10 mg on days 44 through 50, and 5 mg on days 51 through 57). The second group received two weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (125 mg every 6 hours for 72 hours), followed by oral prednisone (60 mg on days 4 through 7, 40 mg on days 8 through 11, and 20 mg on days 12 through 15), with placebo capsules on study days 16 through 57. The third group received placebo, consisting of an equivalent volume of intravenous 5 percent dextrose solution (every 6 hours for 72 hours), followed by placebo capsules on days 4 through 57. Randomization was stratified according to hospital with a permuted-block scheme; 40 percent of the patients were assigned to the placebo group, 30 percent to the eight-week glucocorticoid group, and 30 percent to the two-week glucocorticoid group.

The Veterans Affairs Cooperative Studies Clinical Research Pharmacy Coordinating Center distributed the study medications. Designated research pharmacists dispensed the intravenous medications in a blinded fashion. All patients received the same number of identical-appearing study capsules in blister packs. We assessed compliance on the basis of capsule counts.

The patients remained hospitalized for at least three days for intravenous therapy, after which they received capsules of prednisone or placebo for eight weeks. Hospital staff decided the date of discharge after three days of intravenous therapy. All the patients received a broad-spectrum antibiotic for seven days. For the entire six-month period, the patients were required to use an inhaled β-adrenergic agonist (two puffs from a metered-dose inhaler or a nebulizer treatment at least four times daily), inhaled ipratropium bromide (two puffs from a metered-dose inhaler or a nebulizer treatment at least four times daily), and starting on day 4, inhaled triamcinolone acetonide (eight puffs daily in divided doses) or its equivalent. Use of theophylline, high-dose inhaled glucocorticoids (more than eight puffs daily of triamcinolone acetonide or its equivalent), and open-label systemic glucocorticoids was not allowed. Treatment was considered to have failed if any of the forbidden medications were prescribed. Other medications were permitted according to medical need. We evaluated the patients on each of the first three hospital days and at two weeks, eight weeks, and six months. We continued to obtain follow-up data for patients in whom the study drug had been withdrawn because of treatment failure or for other reasons. If a patient missed a visit, we collected data by mail, telephone, or a review of medical records.

End Points

The primary end point, a first treatment failure, was defined as death from any cause or the need for intubation and mechanical ventilation, readmission because of COPD, or intensification of pharmacologic therapy. The patients' primary physicians made all the clinical decisions. We defined intensification of pharmacologic therapy as the prescription of open-label systemic glucocorticoids, high-dose inhaled glucocorticoids (more than eight puffs per day of triamcinolone acetonide or its equivalent), theophylline, or any combination of these three therapies. When multiple failures occurred on the same day, the assignment to the category of first failure was hierarchical, in the following descending order: death, intubation, readmission, and intensification of therapy. When a primary end point (other than death) was reached, the study treatment was terminated, and usual medical care was resumed.

Secondary end points were a change in FEV_1, the length of the hospital stay, and death from any cause during the six months of follow-up. The patients underwent spirometry at base line; on days 1, 2, and 3; and at the two-week, eight-week, and six-month visits. All centers performed spirometry (model 922, SensorMedics, Yorba Linda, Calif.) according to standard recommendations.[12] We calculated the initial hospital stay as the period from the day of admission to the day of discharge or transfer to an extended-care facility.

Complications

We evaluated the patients for any possible adverse effects of treatment at each visit. As described elsewhere,[10] the diagnosis of hyperglycemia, hypertension, secondary infection, upper gastrointestinal bleeding, or acute psychiatric illness required a consultation, an invasive procedure, or initiation of a specific therapy. We also questioned the patients about other possible adverse events.

Statistical Analysis

The base-line characteristics of the patients in the three treatment groups were compared by means of analysis of variance for continuous variables and the chi-square test for categorical variables.[13] All comparisons of results were based on the intention-to-treat principle. Treatment comparisons were made with the use of a two-step procedure: if the findings for the two-week and the eight-week groups were found to be equivalent, these two groups were combined into a single active-treatment group for comparison with placebo. Comparisons were made at 30, 90, and 182 days after the start of treatment. Treatment failure, the primary end point, was analyzed with use of the upper limit of a one-sided 95 percent confidence interval to determine therapeutic equivalence[14] and a two-sided log-rank test to compare differences between curves for the cumulative failure rate.[15] Values for FEV_1 in the glucocorticoid and placebo groups were compared by analysis of variance, and hospital stays were compared with use of the Wilcoxon two-sample rank test.[13] A complication rate was defined as the proportion of patients who had one or more episodes of a complication during the six months of follow-up. Logistic-regression analysis was used

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 271 PATIENTS ACCORDING TO TREATMENT ASSIGNMENT.*

CHARACTERISTIC	PLACEBO (N=111)	GLUCOCORTICOIDS FOR 2 WK (N=80)	GLUCOCORTICOIDS FOR 8 WK (N=80)
Age — yr	67.8±10.0	67.1±10.6	68.1±6.8
Male sex — no.	111	80	77
White race — no.	99	59	68
Cough — no. (%)	65 (59)	41 (51)	43 (54)
Sputum production — no. (%)	74 (67)	54 (68)	52 (65)
Wheezing — no. (%)	98 (88)	70 (88)	72 (90)
No. of chest colds per year — no. (%)			
None	17 (15)	17 (21)	14 (18)
1 or 2	64 (58)	51 (64)	50 (62)
≥3	30 (27)	12 (15)	16 (20)
Smoked in past 3 mo — no. (%)	56 (50)	42 (52)	40 (50)
Total cigarette smoking — pack-yr	77.0±35.5	67.3±31	80.9±43.8†
Regular medications — no. (%)			
Inhaled beta-adrenergic agonist	96 (86)	66 (83)	72 (90)
Inhaled anticholinergic drug	81 (73)	47 (59)	58 (72)
Oral beta-adrenergic agonist	12 (11)	4 (5)	7 (9)
Theophylline	37 (33)	26 (32)	30 (38)
Inhaled glucocorticoids	49 (44)	39 (49)	40 (50)
Use of oxygen at home — no. (%)	20 (18)	12 (15)	15 (19)
Hospitalization for COPD in previous 2 yr — no. (%)	73 (66)	51 (64)	60 (75)
Prior use of systemic glucocorticoids — no. (%)	52 (47)	30 (38)	46 (58)†
Other illnesses — no. (%)			
Diabetes mellitus	5 (5)	12 (15)	11 (14)†
History of ulcer	23 (21)	19 (24)	16 (20)
Hypertension	44 (40)	39 (49)	39 (49)
Disabling heart disease	13 (12)	8 (10)	8 (10)
Disabling arthritis	12 (11)	10 (12)	15 (19)
History of psychiatric disorder requiring hospitalization	13 (12)	9 (11)	9 (11)
FEV_1 — ml‡	750±271	772±286	785±288
Time from presentation to randomization — hr	3.7±2.6	3.8±2.6	3.7±2.2

*Plus–minus values are means ±SD.

†$P \leq 0.05$ for differences among groups by analysis of variance for continuous variables and by the chi-square test for categorical variables.

‡Data were available for 101 patients in the placebo group, 73 in the two-week glucocorticoid group, and 72 in the eight-week glucocorticoid group.

to identify variables that predicted treatment failure within six months.[15] All reported P values are two-tailed.

RESULTS

Enrollment began in November 1994 and concluded in October 1996, one year ahead of schedule. On the basis of interim analyses, the Veterans Affairs Cooperative Studies Evaluation Committee recommended termination of enrollment at that time.

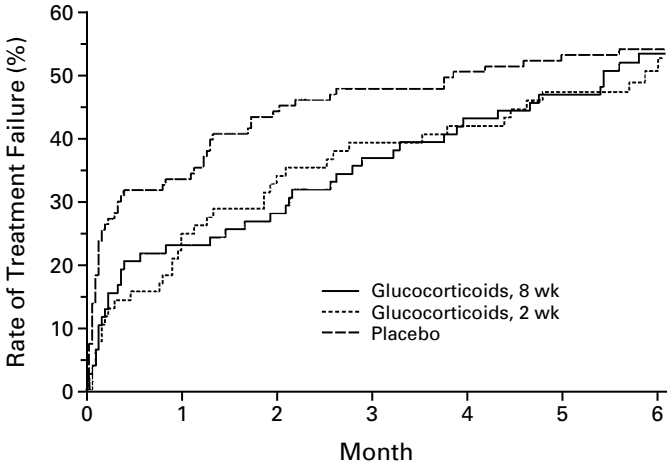
Study Population

A total of 1840 potential patients at 25 Veterans Affairs medical centers were screened for the study, of whom 271 were found to be eligible and were enrolled. The enrollment rate was lower than had been projected,[10] largely because of a substantial decline in admissions for COPD throughout the Veterans Affairs medical system and an unexpectedly high rate of exclusion because of recent use of systemic glucocorticoids. Among the patients who were screened, 49.9 percent had taken systemic glucocorticoids in the previous 30 days. Other common reasons for exclusion included unwillingness or inability to participate (23.2 percent), a history of less than 30 pack-years of smoking (14.6 percent), and coexisting medical conditions expected to limit survival (18.4 percent).

Eighty patients were assigned to receive glucocorticoid therapy for eight weeks, 80 were assigned to receive glucocorticoid therapy for two weeks, and 111 were assigned to receive placebo. The three treatment groups were similar with respect to base-line characteristics (Table 1). There were small differences in total pack-years of cigarette smoking, prior use of systemic glucocorticoids, and the prevalence of diabetes mellitus.

Discontinuation of Study Drugs and Compliance

Study drugs were discontinued for reasons other than a primary end point in 10 patients assigned to placebo (9 percent), 10 assigned to two weeks of



No. at Risk				
Glucocorticoids, 8 wk	80	61	50	21
Glucocorticoids, 2 wk	80	59	46	20
Placebo	111	74	58	39

Figure 1. Kaplan–Meier Estimates of the Rate of First Treatment Failure at Six Months, According to Treatment Group.

glucocorticoids (12 percent), and 5 assigned to eight weeks of glucocorticoids (6 percent). Follow-up data were complete for 19 of these 25 patients. All available data were included in the analyses. On the basis of counts of returned study capsules, the compliance rate was 89 percent in the placebo group, 85 percent in the two-week glucocorticoid group, and 87 percent in the eight-week glucocorticoid group.

Primary Outcomes

Figure 1 shows Kaplan–Meier estimates of rates of first treatment failure for the three study groups, and Table 2 shows the reasons for treatment failure at 30, 90, and 182 days. At least one treatment failure occurred in approximately half the patients. Intensification of therapy was the most common reason for treatment failure, accounting for 70 percent of the total failures at 30 days, 62 percent at 90 days, and 58 percent at 182 days. When therapy was intensified, physicians administered open-label systemic glucocorticoids in more than 75 percent of cases.

The trial did not demonstrate equivalence of outcomes at any time. When the upper limits of one-sided confidence intervals are used to compare failure rates between groups, the results show that the withholding of glucocorticoids may have increased treatment-failure rates by as much as 20 percent at 30 days, 21 percent at 90 days, and 12 percent at 182 days. All values exceeded the limit of 7.5 percent set by the protocol.

As compared with placebo, glucocorticoids significantly reduced the rate of first treatment failure at 30 days (23 percent vs. 33 percent, $P=0.04$) and 90 days (37 percent vs. 48 percent, $P=0.04$) (Table 2). Treatment-failure rates did not differ significantly at six months (51 percent in the combined glucocorticoid groups vs. 54 percent in the placebo group, $P=0.58$). The duration of glucocorticoid therapy (two weeks or eight weeks) had no significant effect on the rate of treatment failure at any time.

Length of Hospitalization

The average length of the initial hospitalization was significantly longer in the placebo group than in the combined glucocorticoid groups (9.7 vs. 8.5 days, $P=0.03$). After the initial hospitalization, patients in the placebo group spent an average of 2.0 days in the hospital because of COPD, as compared with 1.9 days for patients in the glucocorticoid groups ($P=0.98$). Glucocorticoid-treated patients, on average, spent more time in the hospital for reasons other than COPD than did patients receiving placebo (4.4 vs. 1.2 days, $P=0.07$).

Spirometric Findings

FEV_1 improved significantly faster in the patients who received systemic glucocorticoids than in those who received placebo (Fig. 2). The maximal difference, approximately 0.10 liter, was evident by the first day after enrollment. By the end of two weeks, FEV_1 did not differ significantly between the active-treatment and placebo groups.

TABLE 2. CUMULATIVE PRIMARY OUTCOMES ACCORDING TO TREATMENT ASSIGNMENT.

OUTCOME	PLACEBO (N=111)	GLUCOCORTICOIDS FOR 2 WK (N=80)	GLUCOCORTICOIDS FOR 8 WK (N=80)	P VALUE*
	number (percent)			
30 days				
Death	3 (3)	0	2 (2)	
Intubation	3 (3)	2 (2)	1 (1)	
Readmission for COPD	5 (5)	4 (5)	2 (2)	
Intensification of therapy	26 (23)	13 (16)	13 (16)	
Total	37 (33)	19 (24)	18 (22)	0.04
90 days				
Death	4 (4)	2 (2)	2 (2)	
Intubation	3 (3)	3 (4)	1 (1)	
Readmission for COPD	13 (12)	8 (10)	6 (8)	
Intensification of therapy	33 (30)	17 (21)	20 (25)	
Total	53 (48)	30 (38)	29 (36)	0.04
182 days				
Death†	4 (4)	2 (2)	3 (4)	
Intubation	3 (3)	3 (4)	2 (2)	
Readmission for COPD	17 (15)	12 (15)	13 (16)	
Intensification of therapy	36 (32)	22 (28)	24 (30)	
Total	60 (54)	39 (49)	42 (52)	0.58

*P values are for comparisons of the placebo group with the combined glucocorticoid groups, by the log-rank test.

†Only deaths that were counted as primary outcomes are listed. The total numbers of deaths during six months of follow-up were 11 in the placebo group and 13 in the glucocorticoid groups.

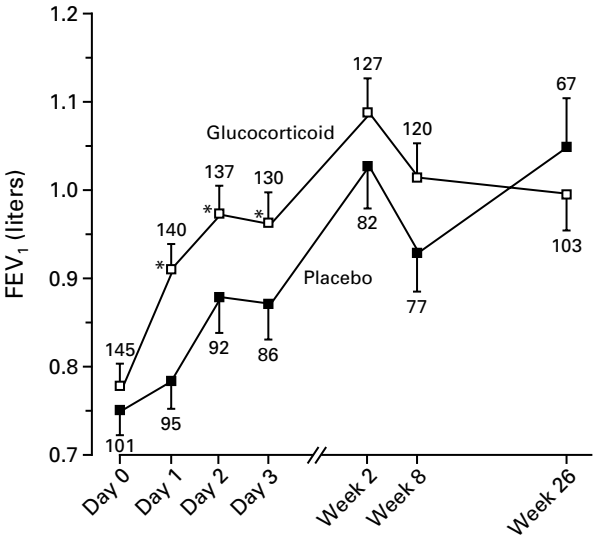


Figure 2. Mean Forced Expiratory Volume in One Second (FEV_1) at Selected Times According to Treatment Group.

The two-week and eight-week glucocorticoid groups have been combined. The numbers at each time point are the numbers of patients in each group for whom data were available. The asterisks denote $P<0.05$ for the comparison with placebo. The bars indicate standard errors.

Death from All Causes

Over the six months of follow-up, 11 of the 111 patients receiving placebo and 13 of the 160 receiving glucocorticoids died (P=0.61). Seven deaths in the placebo group and six in the combined glucocorticoid groups were attributed to COPD.

Complications

Table 3 shows the reported complications for each treatment group over the six months. A greater proportion of patients in the glucocorticoid groups than in the placebo group had hyperglycemia requiring treatment (15 percent vs. 4 percent, P=0.002). Twenty-two of the 24 episodes in the glucocorticoid groups occurred during the first 30 days of follow-up. Sixteen of the 24 glucocorticoid-treated patients with hyperglycemia were known to have diabetes. The patients who received glucocorticoids also had more adverse events classified as "other" (P=0.04); these included 41 separate symptoms or conditions, most of which were not thought to be caused by glucocorticoids. Reported rates of secondary infection did not differ significantly among the three groups, but the eight-week glucocorticoid group had the highest proportion of patients with serious infections. Eleven of the patients in this group were rehospitalized with a primary diagnosis of infection; 9 of the 11 had pneumonia. Only four patients in the placebo group and one in the two-week glucocorticoid group were rehospitalized for infection.

TABLE 3. COMPLICATIONS OF TREATMENT DURING THE SIX-MONTH FOLLOW-UP PERIOD.

COMPLICATION	PLACEBO (N=111)	GLUCOCORTICOIDS FOR 2 WK (N=80)	GLUCOCORTICOIDS FOR 8 WK (N=80)	P VALUE*
	number (percent)			
Hyperglycemia	4 (4)	14 (18)	10 (12)	0.002
Gastrointestinal bleeding	5 (5)	0	3 (4)	0.21
Secondary infection	19 (17)	12 (15)	18 (22)	0.73
Hypertension	4 (4)	6 (8)	4 (5)	0.33
Psychiatric disorder	3 (3)	5 (6)	2 (2)	0.47
Other adverse events†	16 (14)	18 (22)	21 (26)	0.04

*P values are for comparisons of the placebo group with the combined glucocorticoid groups, by the chi-square test.

†This category includes 41 different symptoms or conditions.

Subgroup Analyses

As specified by the protocol, we performed subgroup analyses for the following variables: base-line FEV_1, theophylline use before randomization, hospi-

talization because of COPD in the previous two years, a history of cough, a history of wheezing, a history of sputum production, and a history of chest colds. Multiple logistic regression indicated that a base-line value for FEV_1 that was less than the median value of 0.73 liter predicted a higher rate of treatment failure at 182 days (odds ratio, 1.8; 95 percent confidence interval, 1.1 to 3.1), as did theophylline use before randomization (odds ratio, 2.3; 95 percent confidence interval, 1.3 to 4.0). Only prior hospitalization because of COPD had a significant interaction with the treatment assignment ($P=0.01$). Treatment with glucocorticoids was associated with a more favorable outcome in the group of 184 patients who had previously been hospitalized because of COPD than in the group of 87 with no history of hospitalization because of COPD (odds ratio, 4.6; 95 percent confidence interval, 1.4 to 14.8). In the group of previously hospitalized patients, the failure rate at six months was 66.7 percent for those who received placebo and 49.5 percent for those who received glucocorticoids.

DISCUSSION

We found that the withholding of systemic glucocorticoids was not equivalent to active treatment for hospitalized patients with COPD. Glucocorticoids were marginally superior to placebo in reducing rates of treatment failure at 30 and 90 days, but not at 6 months. Glucocorticoid therapy also shortened the initial hospital stay by an average of 1.2 days. This difference may be an underestimate, because the protocol required a hospital stay of at least three days and because some patients assigned to receive placebo also received open-label glucocorticoids.

Glucocorticoid-induced improvements in FEV_1 provide a plausible basis for the better clinical outcomes. The magnitude of the early effect of treatment on FEV_1, approximately 0.10 liter, is similar to that found in a previous study.[3] More patients received open-label glucocorticoids as the study progressed, so we may have underestimated the true differences at later times.

Hyperglycemia of sufficient severity to require therapy was the major complication of glucocorticoids that we identified. This finding may be due in part to the higher proportions of patients with diabetes in the glucocorticoid groups than in the placebo group, but hyperglycemia is a known complication of glucocorticoid therapy.[16,17] We also noted a trend toward longer hospital stays for causes other than COPD in both glucocorticoid groups. Careful review of these data revealed an unusual number of infections requiring hospital readmission in the eight-week glucocorticoid group. Controlled trials of treatment for other diseases have shown an increased risk of serious infection in patients receiving systemic glucocorticoids.[16,18]

Osteoporosis was not evaluated in this trial, but even relatively brief courses of systemic glucocorticoids cause reductions in trabecular bone mineral density.[19] The cumulative effects of long-term therapy confer a substantial risk of painful vertebral fractures and other long-term complications.[7,20]

Intensification of pharmacologic therapy accounted for more than half of all treatment failures at six months and an even higher proportion during the early weeks of follow-up in our study. Open-label glucocorticoids were administered in most of these cases. Thus, the principal consequence of withholding glucocorticoids in patients receiving placebo was to delay their administration to about half of these patients. The other half recovered and received no glucocorticoids during the full six months of follow-up.

The overall exposure to glucocorticoids among patients hospitalized for COPD would be substantially decreased if the drug were withheld until it was evident that other therapy had failed. The disadvantages of this option are a delay in the administration of effective therapy to patients with severe dyspnea and a prolongation of the average hospital stay by slightly more than a day.

Recent use of systemic glucocorticoids disqualified half the patients screened for this study, and these patients might have had different responses to glucocorticoids. We designed this study specifically for hospitalized patients, reasoning that the effect of treatment would be most evident in the sickest patients. However, systemic glucocorticoids are also frequently used for outpatient treatment of COPD, and the clinical profiles of nonhospitalized patients may be different.

We conclude that systemic glucocorticoids decrease the rate of treatment failure by about 10 percentage points for up to 90 days when used for patients hospitalized with exacerbations of COPD. A two-week regimen was as effective as an eight-week regimen; this result was consistent with those of small trials involving patients with acute asthma.[21,22] In addition, subgroup analyses suggest that the treatment benefit may be restricted largely to patients who have previously been hospitalized because of COPD.

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APPENDIX

The other study participants were as follows: Planning Committee: S. Weiss, J. Stoller, I. Tager, M. Antonelli, and M. Buchanan; Data Monitoring Board: D. Dantzker (chair), D. Tashkin, R. Simon, and M. Lebowitz; Pharmacy coordinator: J. Day; investigators at individual Veterans Affairs medical centers: J. Curtis (principal investigator) and C. Siegert, Ann Arbor, Mich.; G. Emmanuel (coprincipal investigator), S. Carranza (coprincipal investigator), and D. Johnson, Bay Pines, Fla.; P. Romano (coprincipal

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