A CONTROLLED TRIAL OF EARLY ADJUNCTIVE TREATMENT WITH CORTICOSTEROIDS FOR *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

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Abstract *Background.* *Pneumocystis carinii* pneumonia remains a common cause of serious morbidity and mortality in patients with the acquired immunodeficiency syndrome (AIDS). The extensive lung injury that accompanies pneumocystis-associated respiratory failure and the reports of clinical benefit from the use of adjunctive corticosteroids provided the rationale for this prospective multicenter trial.

Methods. A total of 333 patients with AIDS and pneumocystis pneumonia received standard treatment and were randomly assigned to receive either corticosteroids (beginning with the equivalent of 40 mg of prednisone twice daily) or no additional therapy. The primary end points in this unblinded trial were the occurrence of respiratory failure (hypoxemia ratio [partial pressure of arterial oxygen divided by fraction of inspired oxygen] <75, intubation, or death), death, and dose-limiting toxicity of the initial standard therapy.

Results. Of the patients with confirmed or presumed pneumocystis pneumonia (n = 225 and n = 26, respectively), those assigned to treatment with corticosteroids had a lower cumulative risk at 31 days of respiratory failure (0.14 vs. 0.30, P = 0.004) and of death (0.11 vs. 0.23, P = 0.009), as well as a lower risk of death within 84 days (0.16 vs. 0.26, P = 0.026). The frequency of dose-limiting toxicity of the standard therapy was similar in the two treatment groups. Intention-to-treat analyses of the entire cohort confirmed these findings. Clinical benefit could not be demonstrated, however, for patients with mild disease (hypoxemia ratio, >350), equivalent to a partial pressure of oxygen >75 torr on room air. The patients assigned to corticosteroid treatment had an excess of localized herpetic lesions (26 percent vs. 15 percent, P = 0.04) but not of other infections or of neoplasms.

Conclusions. Early adjunctive treatment with corticosteroids reduces the risks of respiratory failure and death in patients with AIDS and moderate-to-severe pneumocystis pneumonia. Because the adverse effects are few, corticosteroids should be included as part of the initial treatment for persons with AIDS who have moderate-to-severe pneumocystis pneumonia. (N Engl J Med 1990; 323:1451-7.)

PNEUMOCYSTIS CARINII pneumonia remains a common cause of serious morbidity and mortality in patients with the acquired immunodeficiency syndrome (AIDS).[1-8] The extensive lung injury found in patients with respiratory failure due to pneumocystis pneumonia and the antiinflammatory actions of corticosteroids provide a rationale for evaluating the efficacy of adjunctive treatment with corticosteroids.[9-16] Clinical evidence in patients who do not have AIDS suggests that although corticosteroids increase the vulnerability to pneumocystis pneumonia, they may reduce the symptoms of infection.[17,18] In patients with AIDS and pneumocystis pneumonia, reports have suggested that adjunctive treatment with corticosteroids can reduce signs and symptoms, improve lung function, and increase tolerance for antipneumocystis therapy.[19-27]

Although physiologic benefit from adjunctive treatment with corticosteroids has been documented, prospective studies must establish improvement in clinical outcomes, particularly given the concern that corticosteroids may result in the exacerbation or development of opportunistic conditions.[28-31] We conducted a multicenter, randomized, controlled trial of the use of early adjunctive corticosteroids in patients with human immunodeficiency virus (HIV) infection and pneumocystis pneumonia.

METHODS

Patient Selection

The patients had received fewer than 36 hours of therapy for HIV-related pneumocystis pneumonia that was either presumed or confirmed. Patients were excluded from the study if they were under 18 years of age or had a documented intolerance to corticosteroids. They were also excluded if they were receiving mechanical ventilation or had a hypoxemia ratio of less than 75. The hypoxemia ratio was calculated as the partial pressure of arterial oxygen divided by the fraction of inspired oxygen. All the patients gave written in-

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formed consent before enrollment. The protocol and consent forms were reviewed and approved by the institutional review boards at each institution.

Study Design

This was a randomized, nonblinded clinical trial. The patients were stratified according to center, initial form of antipneumocystis therapy, and severity of illness, as indicated by their initial hypoxemia ratio. The severity strata were defined as follows: stratum 1, mild (hypoxemia ratio, >350); stratum 2, moderate (hypoxemia ratio, >250 and ≤350); and stratum 3, severe (hypoxemia ratio, ≤250 but >75). The randomization was prepared centrally, with blocks of four patients per stratum and a 1:1 proportion; it was carried out by means of sealed envelopes at the study sites.

The patients were treated with the form of standard therapy selected by their primary physicians. The acceptable standard treatments were oral or parenteral trimethoprim–sulfamethoxazole (15 to 20 mg of the trimethoprim component per kilogram of body weight per day), parenteral pentamidine (3 to 4 mg per kilogram per day), or oral dapsone (100 mg per day) plus trimethoprim (15 to 20 mg per kilogram per day). The patients randomly assigned to corticosteroid treatment received prednisone (40 mg twice a day for five days, followed by 40 mg daily for five days, followed by 20 mg daily for the duration of antipneumocystis therapy). Patients unable to take oral medication received parenteral methylprednisolone (75 percent of the respective prednisone doses). Patients considered by their physicians to have had no response or to have had intolerance to the initial therapy could be switched to another form of standard therapy. Patients in whom respiratory failure developed could receive corticosteroids on the orders of their primary physicians.

Patients were classified as negative for the disease if no *P. carinii* was found when adequate specimens obtained at bronchoscopy were examined by standard techniques. Patients who did not undergo these procedures or for whom the diagnosis was not confirmed by examination of sputum were classified as having presumed disease. Patients for whom there was morphologic confirmation of the diagnosis according to the standard criteria used by the pathologists at each participating center were classified as having confirmed disease.

Assessments and End Points

The patients were evaluated at base line and on study days 3, 6, 10, 14, 21, and 84 for the presence of fever (temperature, >38°C [100.5°F]), respiratory symptoms, the occurrence and progression of other disease, and untoward effects of drug treatment. The laboratory evaluation included a random determination of the base-line cortisol level, serial measurements of arterial blood gases, and complete blood counts.

The primary end point of the study was respiratory failure, which was defined as being indicated by death, the institution of mechanical ventilation, or a hypoxemia ratio of less than 75 at a scheduled evaluation (equivalent to a partial pressure of arterial oxygen of less than 60 torr, with a mask delivering 80 percent oxygen). The secondary end points were death and toxicity from antipneumocystis therapy sufficient to necessitate the termination of treatment.

Statistical Analysis

The calculation of sample size called for a total of 240 patients with confirmed pneumocystis pneumonia, in order to permit the detection of a reduction in the risk of an unfavorable outcome from 30 percent to 15 percent, with a beta error of 0.20 and a two-tailed alpha error of 0.05. We estimated that 340 patients would be needed to ensure the recruitment of 240 patients with confirmed disease.

The treatment groups were compared by the chi-square test, the t-test, or the Mann–Whitney statistic, as appropriate. The Mantel–Haenszel procedure was used as appropriate to adjust for center.[32] Survival curves were produced by the Kaplan–Meier product-limit method, and the risks of unfavorable outcomes were compared by the Wilcoxon test.[33] Univariate Cox models were used to derive estimated relative hazards for the survival data.[34] The effects of base-line covariates on the risks of unfavorable outcomes were determined by fitting Cox proportional-hazards models.[35] Significant predictors were identified by an examination of the global chi-square of the log-likelihood ratios in a series of models. The occurrence of symptoms and signs was evaluated by comparing the proportions of observations during which the sign or symptom was present in each treatment group. Distance-weighted least-squares smoothing was used to estimate the risk of an unfavorable outcome across a range of partial pressures of oxygen as measured at presentation.[36]

Results

Subjects

Between June 17, 1987, and June 16, 1989, 333 patients were entered in the randomized trial. Five patients did not meet the criteria for entry into the study because they already had respiratory failure. Seventy-seven were classified as negative for pneumocystis pneumonia, and 26 were classified as having presumed disease. Of these 26, 13 (50 percent) had respiratory failure before bronchoscopy could be performed, and 11 of these 13 (85 percent) subsequently died. The remaining 225 patients had confirmed pneumocystis pneumonia.

The most clinically relevant group of enrollees excluded only the 82 patients who either did not meet the entry criteria or were demonstrated to be negative for pneumocystis pneumonia. Therefore, this report focuses on the 251 patients with confirmed or presumed disease (225 and 26 patients, respectively). Of these patients, 123 (49 percent) were assigned to receive standard therapy plus adjunctive corticosteroids and 128 (51 percent) to receive standard treatment alone. The base-line characteristics of the two treatment groups were similar (Table 1). In the corticosteroid group, one (1 percent) and three (2 percent) patients were lost to follow-up after 21 and 84 days of the study, respectively; in the standard-treatment group, five (4 percent) and seven (6 percent) patients were lost after the corresponding intervals.

Occurrence of Unfavorable Outcomes

Forty-one of the 251 patients (16 percent) died during the acute episode of pneumocystis. One death was due to sepsis with *Staphylococcus aureus;* the other 40 deaths were related to pneumocystis pneumonia. Seven additional patients received mechanical ventilation, and in seven more hypoxemia ratios of less than 75 were recorded at a scheduled evaluation, but the patients were not intubated. Thus, respiratory failure occurred in 55 of the 251 patients (22 percent). Thirty-seven of these events (67 percent) took place during the first four days on which the patient was studied.

The cumulative risks of respiratory failure on day 21 (the last scheduled evaluation of the acute episode) were 0.13 and 0.28 in the corticosteroid and the standard-treatment groups, respectively ($P = 0.004$). The cumulative risks of death were 0.09 and 0.18, respectively ($P = 0.024$) (Fig. 1). The corresponding cumulative risks at the time of the last pneumocystis-related death on day 31 were 0.14 in the corticosteroid group

Table 1. Base-Line Characteristics of 251 Patients with Presumed or Confirmed Pneumocystis Pneumonia, According to Treatment-Group Assignment.

CHARACTERISTIC	TREATMENT GROUP*	
	CORTICOSTEROIDS	STANDARD THERAPY
No. of patients	123	128
Age (yr)	36±9	36±8
	number (percent)	
Treatment center		
1	51 (41)	53 (41)
3	39 (32)	42 (33)
2, 4–6	33 (27)	33 (26)
Stratum		
1	28 (23)	34 (26)
2	60 (49)	61 (48)
3	35 (28)	33 (26)
Male sex	118 (97)	125 (98)
Homosexual behavior†	94 (85)	97 (88)
Intravenous drug use†	16 (15)	13 (12)
Race or ethnic group‡		
White	84 (68)	85 (66)
Black	13 (11)	17 (13)
Hispanic	22 (18)	21 (16)
Previous AIDS-defining opportunistic infections		
Pneumocystis pneumonia	24 (20)	29 (23)
Kaposi's sarcoma	19 (15)	12 (9)
Other	12 (10)	8 (6)
Zidovudine treatment§	11 (16)	9 (14)
Symptoms	22±23	19±19
Duration (days)		
Cough	114 (93)	119 (93)
Fever	113 (92)	113 (88)
Dyspnea at rest	84 (68)	85 (66)
Chest pain	45 (37)	53 (41)
Hemoglobin (g/liter)	117±20	120±21
Leukocytes ($\times 10^{-9}$/liter)	6.3±3.5	6.3±2.8
Platelets ($\times 10^{-9}$/liter)	280±104	286±124
Cortisol (nmol/liter)	552±235	607±221
Hypoxemia ratio	295±78	308±77
Bronchoscopy	93 (76)	95 (74)
Hospitalization	116 (94)	125 (98)
Supplemental oxygen therapy	96 (78)	102 (80)
Initial therapy		
Trimethoprim–sulfamethoxazole	98 (80)	103 (80)
Pentamidine	22 (18)	23 (18)
Dapsone/trimethoprim	3 (2)	2 (2)

*Plus–minus values are means ±SD. All other values are numbers of patients (percent).

†Data for this variable are based on studies of 110 patients in each treatment group.

‡Because of missing information, data on race and ethnic group are based on 119 patients in the corticosteroid group and 123 patients in the standard-therapy group.

§Data for this variable are based on studies of 67 patients in the corticosteroid group and 65 patients in the standard-therapy group.

and 0.30 in the standard-treatment group for respiratory failure (P = 0.004) and 0.11 and 0.23, respectively, for death (P = 0.009) (Fig. 1). The cumulative risks of death on day 84 were 0.16 and 0.26, respectively (P = 0.026).

The cumulative risk of dose-limiting toxicity from antipneumocystis therapy after 21 days was 0.22 in the corticosteroid group and 0.31 in the standard-treatment group (P = 0.12). However, the median duration of therapy, which indicates both efficacy and toxicity, was longer in the corticosteroid group among the 201 patients (80 percent) initially treated with trimethoprim–sulfamethoxazole (20.5 vs. 14 days for the standard-treatment group, P = 0.002). Sixty-nine of 98 such patients in the corticosteroid group (70 percent) completed at least 14 days of therapy, but only 56 of 103 patients in the standard-treatment group (54 percent) did so (P = 0.03).

In both treatment groups, the crude risk of an unfavorable outcome was low for the patients in stratum 1, who were less severely ill (Table 2). This risk and the difference in risk between the two treatment groups increased with increasing severity of disease (Table 2 and Fig. 2).

The patients taking corticosteroids had a lower risk of respiratory failure and death in the subsidiary analyses of all 333 patients enrolled (the intention-to-treat analysis), of the 328 eligible patients, and of the 225 patients with confirmed pneumocystis pneumonia (Table 3). Trends indicating a benefit from corticosteroids were also observed in each subgroup in an analysis performed according to center and type of initial antipneumocystis therapy.

Effect on Signs and Symptoms

The symptoms that were observed less often in the corticosteroid group than in the standard-treatment group included fever (34 percent vs. 49 percent, P<0.001), cough (54 percent vs. 68 percent, P<0.001), and dyspnea at rest (29 percent vs. 40 percent, P = 0.01). Chest pain was present to a similar extent in the two treatment groups (25 percent vs. 28 percent, P = 0.16). None of the recorded symptoms were more frequent in the corticosteroid group.

Incidence of Other Conditions and Recurrence

After 84 days of study, there was a higher incidence of focal reactivation of herpesviruses in the corticosteroid group (32 of 123 patients, or 26 percent) than in the standard-treatment group (19 of 128 patients, or 15 percent; P = 0.04) (Table 4). There was also a trend toward an increase in the incidence of oral thrush after 84 days (Table 4). The incidence of other HIV-associated opportunistic conditions was similar in both treatment groups after both 21 and 84 days of follow-up (Table 4). The effect of corticosteroids on

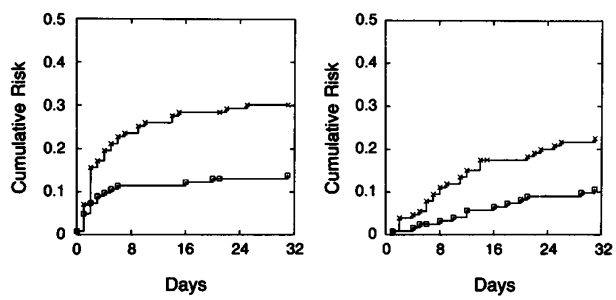

Figure 1. Cumulative Risk of an Unfavorable Outcome over a Period of 31 Days.

The risk of respiratory failure (left panel) was 0.14 in the corticosteroid group (□) and 0.30 in the standard-treatment group (×) (P = 0.004). The risks of death (right panel) were 0.11 and 0.23, respectively (P = 0.009).

Table 2. Crude Risk of an Unfavorable Outcome after 31 Days of Follow-up, According to Severity of Pneumocystis Pneumonia.

CHARACTERISTIC*	DISEASE STRATUM			
	1 (MILD)	2 (MODERATE)	3 (SEVERE)	ALL
	number (percent)			
Patients				
All	62	121	68	251
Standard therapy	34 (55)	61 (50)	33 (49)	128 (51)
Corticosteroids	28 (45)	60 (50)	35 (51)	123 (49)
Respiratory failure				
Standard therapy	3 (9)	19 (31)	16 (48)	38 (30)
Corticosteroids	1 (4)	7 (12)	9 (26)	17 (14)
Relative risk (95% CI)	2.5 (0.2–69.0)	2.7 (1.3–5.6)	1.9 (1.0–3.6)	2.3 (1.4–3.6)
P value	0.38	0.01	0.05	0.001
Death				
Standard therapy	1 (3)†	13 (21)	14 (42)	28 (22)
Corticosteroids	0 (0)	6 (10)	7 (20)	13 (11)
Relative risk (95% CI)	—	2.1 (0.9–5.1)	2.1 (1.0–4.5)	2.2 (1.2–3.9)
P value	0.55	0.09	0.05	0.01

*CI denotes confidence interval.

†This death was attributed to *Staphylococcus aureus* sepsis; all other deaths were attributed directly or indirectly to pneumocystis pneumonia.

the severity of preexisting conditions was not measured systematically.

Information on the use of maintenance therapy and the rate of recurrence of pneumocystis pneumonia after 84 days was available for 178 of the 210 patients who survived the acute episode (85 percent). There were confirmed relapses in 4 of 95 patients (4 percent) in the corticosteroid group and in 4 of 83 patients (5 percent) in the standard-treatment group (P = 0.54), whereas there were unconfirmed relapses in 5 patients (5 percent) and 3 patients (4 percent), respectively (P = 0.80) — a total of nine relapses (9 percent) and seven relapses (8 percent) in the respective groups (P = 0.79).

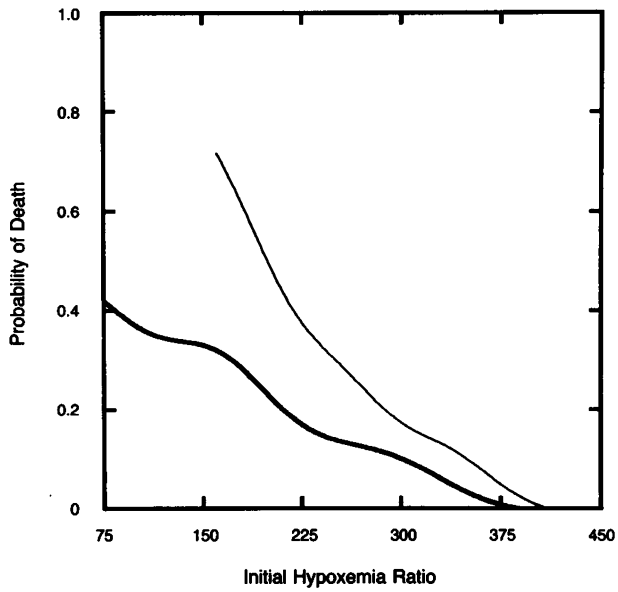

Figure 2. Probability of Death from Respiratory Causes, According to Initial Hypoxemia Ratio.

No deaths from respiratory causes occurred in the patients with hypoxemia ratios above 319 in the corticosteroid group (heavy line) or those with ratios above 342 in the standard-treatment group (light line), but the mathematical function used to smooth the data predicts that at hypoxemia ratios above these levels, some deaths might be expected in a larger sample. For an explanation of the calculation of the hypoxemia ratio, see Methods.

Multivariate Analysis

The effect of corticosteroids in relation to other prognostic factors was examined with multivariate Cox proportional-hazards modeling. The significant independent predictors of respiratory failure were lower hypoxemia ratios at entry and random assignment to standard treatment alone. These variables and enrollment at center 3 were significant independent predictors of death during the acute episode. Covariates that were not independently predictive of either outcome included age, risk group, race, history of pneumocystis pneumonia, symptom duration, type of initial primary treatment, presence of other opportunistic or bacterial infection, and initial concentrations of hemoglobin and cortisol.

Effect on Pulmonary Function

The mean hypoxemia ratio on day 3 of the study declined by 41 in the standard-treatment group but increased by 4 in the corticosteroid group (P = 0.01) (Fig. 3). Thereafter, oxygenation was improved in both groups, with consistently more improvement in the corticosteroid group. The mean change from base line over the 21 days of observation was an increase of 66 in the corticosteroid group and of 17 in the standard-treatment group (P<0.001).

Treatment of Respiratory Failure

Among the patients whose hypoxemia ratio declined to less than 75, mechanical ventilation was used in 5 of 10 (50 percent) in the corticosteroid group and in 15 of 26 (58 percent) in the standard-treatment group (P = 0.48). The patients receiving mechanical ventilation had similar median hypoxemia ratios at the last scheduled arterial blood gas measurement before intubation (205 vs. 214, P = 0.52).

High doses of parenteral corticosteroids were prescribed for "rescue" at the discretion of the primary physician in 7 of 17 patients (41 percent) in the corticosteroid group and 19 of 38 patients (50 percent) in the standard-treatment group in whom respiratory failure developed (P = 0.55). The short-term mortal-

Table 3. Estimated Cumulative Risk of an Unfavorable Outcome, According to Eligibility for the Study and Type of Diagnosis of Pneumocystis Pneumonia.

Characteristic*	Category of Patients			
	All	Eligible	Confirmed or presumed disease	Confirmed disease
No. of patients	333	328	251	225
			percent	
Respiratory failure				
Standard therapy	—	25	30	27
Corticosteroids	—	12	14	11
Relative hazard (95% CI)	—	2.3 (1.3–4.2)	2.3 (1.3–4.3)	2.6 (1.3–5.3)
P value	—	0.003	0.004	0.005
Death after 31 days				
Standard therapy	20	20	23	19
Corticosteroids	10	9	11	8
Relative hazard (95% CI)	1.9 (1.1–3.4)	2.2 (1.2–4.1)	2.3 (1.2–4.4)	2.6 (1.2–5.7)
P value	0.026	0.007	0.009	0.010
Death after 84 days				
Standard therapy	25	25	26	23
Corticosteroids	17	15	16	12
Relative hazard (95% CI)	1.6 (1.0–2.7)	1.8 (1.1–3.0)	1.8 (1.0–3.2)	2.2 (1.1–4.2)
P value	0.039	0.014	0.026	0.015

*CI denotes confidence interval.

ity among the patients who received such therapy after respiratory failure, as compared with that among those who did not, was 11 of 16 (69 percent) as compared with 5 of 7 (71 percent) at center 1 (P = 0.25), 2 of 2 (100 percent) as compared with 15 of 16 (94 percent) at center 3 (P = 0.89), and 4 of 8 (50 percent) as compared with 3 of 6 (50 percent) at all the other centers (P = 0.70). Furthermore, in the 55 patients in whom respiratory failure developed, multivariate Cox modeling showed that neither the original treatment-group assignment nor the use of high-dose corticosteroids was a significant predictor of survival.

Discussion

In this study, the early use of adjunctive corticosteroids in patients with HIV infection and pneumocystis pneumonia was associated with a reduction by approximately half in the risk of acute respiratory failure and death. The benefit in survival persisted over at least 84 days. Outcomes improved for patients with moderate-to-severe lung dysfunction at presentation (Table 2). The benefit appeared to increase with increasing severity of pulmonary dysfunction at presentation (Fig. 3) — a finding corroborated by the strong effect of corticosteroids in a recently concluded double-blind trial in 23 patients with severe pneumocystis pneumonia.[37] In accordance with previous observations, the risk of respiratory failure was low, and no deaths from respiratory causes were observed in the patients who presented with mild disease.[4]

The use of adjunctive corticosteroids did not significantly reduce the treatment-limiting toxicity of antipneumocystis therapy. However, the patients in the corticosteroid group who received trimethoprim – sulfamethoxazole were still more likely to complete an adequate course in the initial antipneumocystis therapy than their counterparts in the standard-treatment group, because the initial therapy was less often discontinued or changed because of treatment failure or a perception of such failure. No adverse effects directly attributable to treatment with corticosteroids were observed, and except for an increase in the reactivation of localized herpetic lesions, there were no significant differences between the treatment groups in the incidence of other morbid conditions.

Because this study was not blinded, there is a possibility that bias may account for these results.[38] Bias in the selection of subgroups for analysis or the ascertainment of end points is ruled out by the significant survival benefit demonstrated in the strict intention-to-treat analysis. Systematic differences in the medical care of patients cannot be ruled out definitively, but several factors make such differences unlikely; among them are the consistent benefit demonstrated at a number of institutions, the consistent use of mechanical ventilation and high-dose corticosteroids for rescue in patients with respiratory failure, and the uniformly poor prognosis of patients with respiratory failure within institutions, regardless of original treatment assignment or use of rescue corticosteroids. Multivariate analysis was used to adjust for possible confounding, but treatment-group assignment remained highly pre-

Table 4. Incidence of Infections and Cancers.

Type of Morbidity*	After 21 Days		After 84 Days	
	Steroids	Standard therapy	Steroids	Standard therapy
	number (percent)			
Thrush†	28 (23)	22 (17)	65 (53)	53 (41)
Herpetic lesions‡	16 (13)	7 (5)	32 (26)	19 (15)
Any serious opportunistic infection	7 (6)	9 (7)	28 (23)	27 (21)
CMV disease	1 (1)	0 (0)	6 (5)	4 (3)
MAI bacteremia	0 (0)	0 (0)	7 (6)	8 (6)
Cryptococcosis	5 (4)	4 (3)	9 (7)	7 (5)
Esophageal candidiasis	1 (1)	4 (3)	5 (4)	7 (6)
Kaposi's sarcoma	0 (0)	1 (1)	12 (10)	11 (9)
Bacterial pneumonia	5 (4)	6 (5)	8 (7)	7 (6)
Pyogenic bacteremia	0 (0)	2 (2)	2 (2)	4 (3)

*CMV denotes cytomegalovirus, and MAI *Mycobacterium avium–intracellulare*.

†P<0.10 after 84 days.

‡New focal reactivation of herpes simplex virus (in 50 patients) or varicella–zoster virus (in 1 patient) (P<0.10 after 21 days and P<0.04 after 84 days).

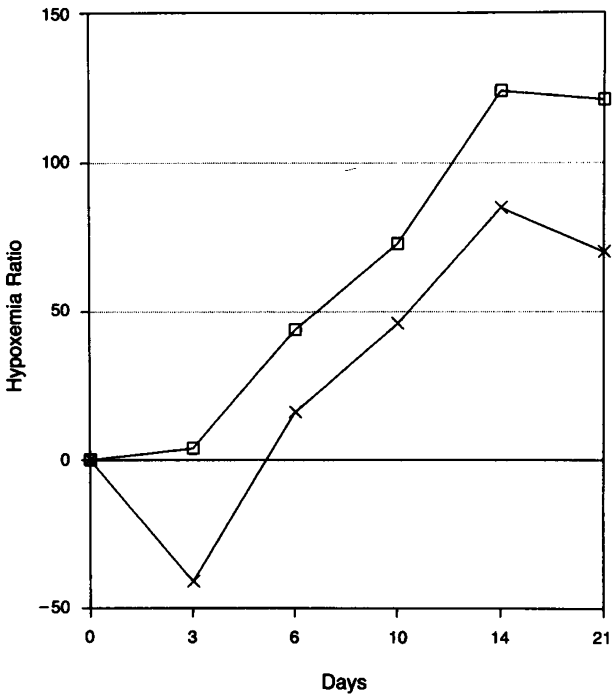

Figure 3. Changes in the Hypoxemia Ratio over Time.
The group means were significantly different on day 3 (4 vs. −41, P = 0.01). The mean of all the difference scores was 66 in the corticosteroid group (□) and 17 in the standard-treatment group (×) (P<0.001). For an explanation of the calculation of the hypoxemia ratio, see Methods.

dictive of outcome. Finally, loss to follow-up was slightly more frequent in the corticosteroid group, but all patients lost to follow-up were well at their last evaluation.

Most cases of respiratory failure occurred in association with early deterioration in oxygenation during the first few days of therapy. Thus, the prevention of such early deterioration appears to provide a physiologic basis for the improvement in clinical outcomes in the corticosteroid group (Fig. 2). This effect is consistent with the protective effect of early corticosteroid administration demonstrated previously in animal models of the respiratory distress syndrome[39] and in patients with pneumocystis pneumonia.[28] Furthermore, the finding of superior oxygenation in the corticosteroid group throughout this study was consistent with a previous report of persistently superior exercise tolerance in patients treated with adjunctive corticosteroids early in their illness.[28]

Over the next decade, approximately 750,000 episodes of pneumocystis pneumonia can be expected to cause more than 175,000 deaths in the United States and Western Europe.[40] The number of cases and fatalities can be reduced by identifying persons at risk and providing them with effective prophylaxis.[41] Our data indicate that mortality attributable to pneumocystis pneumonia can be reduced further by the use of an inexpensive course of adjunctive corticosteroids in persons with moderate-to-severe disease. Initial therapy for HIV-related pneumocystis pneumonia in persons with hypoxemia ratios of less than 350 (equivalent to a partial pressure of oxygen of 74 torr while a person is breathing room air) should include prednisone or its equivalent in the dosages used in this trial. Vigorous attempts should be made to confirm the diagnosis in all such patients, in order to avoid adverse effects related to the masking of unsuspected infections, such as tuberculosis and pulmonary cryptococcosis.

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ALTERED EXPRESSION OF THE RETINOBLASTOMA GENE PRODUCT IN HUMAN SARCOMAS

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Abstract *Background.* The retinoblastoma-susceptibility (Rb) gene is a prototype tumor-suppressor gene originally isolated from patients with heritable retinoblastoma. This gene encodes a nuclear phosphoprotein whose expression is altered in several types of human tumors.

Methods. We studied the expression of the Rb protein in 44 primary and 12 metastatic high-grade human sarcomas by means of immunohistochemical methods and Western blotting. Computerized image analysis was used to quantify the level of Rb gene product in individual tumor cells. The expression of the Rb gene was then correlated with clinical outcome in the patients with primary tumors.

Results. Of the 44 patients with primary sarcomas, 13 (30 percent) had tumors with normal, homogeneous expression of the Rb protein in essentially all tumor cells. Thirty-one patients with primary tumors (70 percent) had altered Rb expression; in 18 (40 percent) the Rb protein was heterogeneously expressed, and in 13 (30 percent) it was detected in fewer than 20 percent of the tumor cells. All 12 of the patients with metastatic sarcomas had altered expression of the Rb protein. When the findings in the patients with primary tumors were correlated with clinical outcome, survival was found to be significantly increased in the patients whose tumors had homogeneous Rb expression, as compared with those with either heterogeneous expression ($P = 0.026$) or no expression ($P = 0.012$).

Conclusions. Tumors in which the expression of Rb gene product was decreased were more aggressive than tumors in which this protein was expressed by nearly all cells. The Rb gene product may be an important prognostic variable in patients with these tumors. (N Engl J Med 1990; 323:1457-62.)

THERE is growing evidence of the existence of a family of recessive genes that can promote tumor growth when both alleles are inactivated.[1-4] The prototype of such tumor-suppressor genes is the retinoblastoma-susceptibility (Rb) gene, which is located on human chromosome 13q14[5,6] and encodes a 110-kd nuclear phosphoprotein that is expressed by normal tissues.[7,8] This protein binds DNA[9] and is phosphorylated during the S and G_2–M phases of the cell cycle,[10,11] but its function remains to be elucidated.

The Rb gene was initially found to be deleted in the tumors of patients with heritable retinoblastoma.[12,13] The high incidence of sarcomas in the survivors of this disease suggested that deletion of the Rb gene may be associated with the development of these neoplasms as well.[14,15] Subsequently, either deletions or rearrangements of the Rb gene or altered expression of the Rb gene product have been detected in sarcoma cell lines and some sporadic human sarcomas.[16-18]

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