Corticosteroids as Adjunctive Therapy for Severe *Pneumocystis carinii* Pneumonia in Non–Human Immunodeficiency Virus–Infected Patients: Retrospective Study of 31 Patients

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The aim of this retrospective study was to assess whether corticosteroid adjunctive therapy (CAT) could prevent death in immunocompromised patients with severe *Pneumocystis carinii* pneumonia (PCP) who do not have human immunodeficiency virus (HIV) infection, similarly to what has been demonstrated for HIV-infected patients. The charts of all non-HIV-infected patients who were admitted to two medical intensive care units between 1988 and 1996 because of severe PCP, defined by an arterial oxygen pressure (determined while the patient was breathing room air) of <70 mm Hg, and who were treated with trimethoprim-sulfamethoxazole were analyzed retrospectively. Thirty-one patients met the study criteria, of whom 23 received CAT (within 72 hours of antibiotic therapy) and eight did not receive CAT. The need for mechanical ventilation (10 [43%] of 23 vs. 4 [50%] of 8) and the mortality rate (9 [39%] of 23 vs. 4 [50%] of 8) were similar for the two groups. Although this small study does not have a statistical power high enough to rule out the possibility of a difference, the results suggest that CAT does not improve the survival of non-HIV-infected patients as has been described for HIV-infected patients with severe PCP.

Pneumocystis carinii pneumonia (PCP) is a serious complication in non-HIV-infected immunocompromised hosts. Corticosteroid adjunctive therapy (CAT) markedly improves survival and decreases the need for intubation and mechanical ventilation in markedly hypoxemic patients with AIDS who have PCP [1, 2]. The mortality rate associated with PCP among both HIV-infected and non-HIV-infected populations was demonstrated to be similar before CAT [3, 4]. Whether corticosteroid therapy would similarly benefit non-HIV-infected patients with severe PCP remains to be established, since studies of non-HIV-infected patients have conflicting results [5]. However, PCP is an uncommon disease in non-HIV-infected patients, which makes a prospective, randomized study of CAT almost unfeasible.

To assess whether CAT could have a beneficial effect similar to that documented for HIV-infected patients in terms of reduction of mechanical ventilation and mortality rates, we retrospectively studied a series of non-HIV-infected immunocompromised patients with severe PCP who did or did not receive corticosteroid therapy in addition to standard antimicrobial therapy.

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Patients and Methods

We retrospectively reviewed the charts of all consecutive non-HIV-infected patients with PCP diagnosed from 1988 through 1996 in the medical intensive care units of Hôpital Henri Mondor, Créteil, France, and Hôpital Saint Louis, Paris.

Patients were eligible for inclusion in the study when they met the criteria used by Gagnon et al. [2] in a study of adjunctive corticosteroid therapy for PCP in HIV-infected patients. They were included in the cohort if they met all of the following criteria: negative HIV status, as determined by ELISA; a diagnosis of PCP that was based on demonstration of typical organisms in specimens of bronchoalveolar lavage (BAL) fluid, with no other infecting organism demonstrated by gram staining or culture; significant hypoxemia (Pao_2, <70 mm Hg [measured while the patient was breathing room air]) before institution of therapy (patients who had already undergone endotracheal intubation at the time of diagnosis were excluded from the study); therapy with trimethoprim-sulfamethoxazole, at a dosage of 15–20 mg of trimethoprim/(kg · d), instituted within 48 hours of BAL; and CAT instituted within the first 72 hours of antibiotic treatment.

Severity of acute illness was assessed by the Simplified Acute Physiologic Score (SAPS), which summarizes physiological disturbances and is calculated within the first 24 hours of hospitalization in the intensive care unit [6]. The density of *Pneumocystis* organisms seen during examination of BAL fluid was graded as "many" when foamy alveolar casts were easily visualized (all slides) and "few" when foamy alveolar casts

Table 1. Characteristics of and outcomes for patients without AIDS who did or did not receive CAT for *Pneumocystis carinii* pneumonia.

Finding	Patients who received CAT (n = 23)	Patients who did not receive CAT (n = 8)
Mean Pao_2 ± SD (mm Hg)*	49 ± 10	43 ± 14
Mean SAPS† ± SD	11 ± 4	12 ± 5
No. with underlying disease		
Hematologic malignancy	18‡	6
Vasculitis	2	1
Solid tumor	2	0
Other	1	1
No. (%) with need for mechanical ventilation	10 (43)	4 (50)
No. (%) of deaths	9 (39)	4 (50)

NOTE. CAT = corticosteroid adjunctive therapy; SAPS = Simplified Acute Physiologic Score [6]. There were no significant differences between patients who did or did not receive CAT in terms of initial severity of illness, need for mechanical ventilation, and mortality rate.

* Measured at admission while the patient was breathing room air.

† Measured within 24 hours of admission.

‡ Included three bone marrow recipients.

were not identified after routine examination. In the latter cases, an "improved" yield of *P. carinii* needed careful examination of additional slides that were diligently prepared. It has been suggested that five or more slides should be studied before it is concluded that foamy alveolar casts are absent [7]. This semi-quantitative grading scheme was used because several investigators demonstrated differences in parasite loads in BAL fluid specimens from patients with and without AIDS [3, 4].

For patients receiving CAT, two therapeutic regimens were differentiated: de novo CAT (i.e., "new CAT" for patients who did not receive previous corticosteroid treatment), consisting of either oral prednisone (>1 mg/[kg · d] at institution) or intravenous methylprednisolone (240 mg daily for 3 days followed by 120 mg daily for 3 days and 60 mg daily for 3 days or until the end of antibiotic therapy) [8]; and rescue CAT (i.e., "rescue CAT" for patients already receiving corticosteroid treatment for their underlying disease), where the daily dosage of corticosteroids was increased to at least 300% of the previous dosage (a minimum dosage of 1 mg of oral prednisone/[kg · d] or an equivalent daily dose of methylprednisolone). Although there is no general agreement concerning the dosage and duration of this therapy [9], CAT was always continuous and usually given for the duration of antimicrobial therapy (2 or 3 weeks). CAT doses were tapered according to the scheme of Mottin et al. [8] or over 1 week in the other cases.

Statistical analysis. All data are expressed as means ± SD. χ^2 analysis with continuity correction was used to compare qualitative variables. Intergroup comparisons were performed by nonparametric methods. Statistical significance was defined as $P < .05$.

Results

During the 8-year period of the survey, 38 consecutive patients were eligible for inclusion in the study. No patient had been receiving prophylaxis for PCP. Seven patients with PCP were not included, because they had received delayed (>72 hours) CAT (four patients) or had already undergone endotracheal intubation before diagnosis of PCP (three). Thirty-one patients (15 males and 16 females; mean age ± SD, 49 ± 15 years [range, 16–73 years]) met the criteria for inclusion in the cohort. All patients had immunosuppression (table 1), including 24 (77%) with hematologic disorders. Twenty-three patients received CAT, of whom nine received new CAT and 14 received rescue CAT.

Outcomes for patients who did or did not receive CAT were similar in terms of intubation and mortality rates (table 1). Mortality rates were also similar among patients who received new or rescue CAT (3 [33%] of 9 vs. 6 [43%] of 14, respectively). However, for patients who received CAT, there was a nonstatistically significant trend toward a lower mortality rate among the eight patients with many *Pneumocystis* organisms in their BAL fluid (25%) compared with the 11 patients with fewer organisms in their BAL fluid (63%; $P = .10$), although these two subgroups had similar mean SAPS ± SD at admission (11 ± 5 vs. 10 ± 4, respectively).

Discussion

The mortality rate among our patients who received CAT did not differ from that recorded for patients who did not receive CAT or from those in previously reported series of severe PCP in non-HIV-infected patients who did not receive CAT, where it ranged from 30% to 50% [10]. By contrast, the incidences of mechanical ventilation and death are halved by CAT for AIDS patients with severe PCP, among whom the mortality rate is about 20% to 25% [1, 2]. In the study by Gagnon et al. [2], the inclusion of only 23 patients proved sufficient to demonstrate a

highly statistically significant improvement in survival with CAT. It is interesting that Pareja et al. [5] recently reported a retrospective study of 30 non-HIV-infected adult patients with severe PCP; this study suggested that high-dose adjunctive corticosteroid therapy may accelerate recovery. However, rates of intubation and in-hospital mortality were comparable among patients who did or did not receive CAT. Therefore, outcome for patients was not substantially improved by high-dose CAT in that study, a result that is at variance with the established efficacy of corticosteroid therapy for HIV-infected patients with PCP but is consistent with our findings.

Because of the small number of patients and the retrospective design, our study does not have a statistical power high enough to rule out the possibility of a difference and thus does not allow a firm conclusion about the potential value of steroid therapy for non-HIV-infected patients with severe PCP. However, our results may serve to generate hypotheses. The apparent lack of benefit from corticosteroid therapy for non-HIV-infected patients with PCP, compared with HIV-infected patients, could result from differences in clinical presentation and pathophysiology of disease and/or in underlying disease and immunosuppression in these two populations.

Corticosteroids are thought to attenuate the inflammation associated with drug-induced death of *Pneumocystis* organisms [9], thereby reducing the incidence of acute respiratory distress syndrome complicating severe PCP in AIDS patients. An interesting finding in our study was that the mortality rate tended to be lower among patients with many organisms in their BAL fluid than among patients with few organisms in their BAL fluid (25% vs. 63%, respectively; $P = .10$), despite the fact that these two subgroups had comparable disease severity at admission to the intensive care unit. Although the association between a higher number of *P. carinii* in BAL fluid and a potential benefit from corticosteroid therapy for our non-HIV-infected patients did not reach statistical significance, it is tempting to parallel these findings with the usual effectiveness of corticosteroid therapy for AIDS patients. By contrast to non-HIV-infected patients, AIDS patients with PCP often have high numbers of *P. carinii* in BAL fluid at presentation [3, 4]. Compared with HIV-infected patients, lung inflammation and its worsening with antibiotic therapy therefore may be much less in non-HIV-infected patients with PCP and a low microbial burden in the lung, thus limiting the potential value of CAT.

Another possible explanation for the lack of efficacy of CAT for non-HIV-infected patients with PCP could be prior administration of corticosteroid therapy, which itself is the major risk factor for PCP in this population. Previous immunosuppressive therapies (both steroid and cytotoxic drugs) may alter the response to further CAT. Accordingly, Arend et al. [11] found a significantly higher mortality rate among patients with PCP who had received previous chemotherapy and a trend toward a higher mortality rate among patients with previous corticosteroid use.

Finally, non-HIV-infected patients with PCP constitute a nonhomogeneous group of patients who also could have various associated lung diseases, especially drug- or radiation-induced pneumonitis, and therefore present with respiratory failure due to various reasons, some of which may be associated with a higher risk of treatment failure and mortality. This possibility is consistent with recent findings by Yale and Limper [12], who showed that the mortality rate associated with PCP with respiratory failure was 100% among patients with solid tumor as the underlying disease and only 43% among organ transplant recipients.

Our observations in non-HIV-infected immunocompromised patients with severe PCP, most of whom had hematologic disorders, suggest that corticosteroid therapy at least does not have the dramatic effect observed in AIDS patients, in whom it may prevent the need for mechanical ventilation or death. However, a potential beneficial effect of CAT cannot be excluded in some non-HIV-infected patients; this effect could be masked in this heterogeneous population by clinical presentation (more acute illness), microbiological and pathophysiological features (fewer organisms), or underlying immunosuppression.

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