When Is It Safe to Stop *Pneumocystis jiroveci* Pneumonia Prophylaxis? Insights From Three Cases Complicating Autoimmune Diseases

ANIL SURYAPRASAD1 AND JOHN H. STONE2

**Introduction**

*Pneumocystis jiroveci* pneumonia (PCP) was the first opportunistic infection described during the burgeoning epidemic of human immunodeficiency virus (HIV) in the early 1980s (1). In HIV disease, the extensive morbidity and high mortality caused by this organism led to the development of specific guidelines for its prevention and treatment (2). For example, several studies have demonstrated the clinical benefit and cost-effectiveness of primary prophylaxis against PCP infection for individuals with HIV infection who have oropharyngeal candidiasis or a CD4 T lymphocyte count \(<200/\text{mm}^3\) (3). In addition, for patients who respond to highly active antiretroviral therapy, continuation of PCP prophylaxis is recommended until the CD4 count rises above 200/\text{mm}^3 for 3–6 consecutive months (4).

These guidelines provide clear direction for clinicians and have contributed to a dramatic reduction in morbidity and mortality from PCP in patients with HIV infection (4). Similar progress has been made in the prophylactic treatment of PCP infections among patients who have undergone organ transplantation or who are receiving treatment for cancer (5–8). However, HIV is the only condition in which the peripheral CD4 count has been proven to accurately reflect the degree of depletion of CD4 T lymphocytes within lymphoid tissue.

Despite the availability of effective agents for PCP prophylaxis, studies suggest that there remains a significant disease burden from PCP among patients with autoimmune disorders (9–11). In fact, the mortality rate among patients with rheumatic disease who develop PCP is far higher than that of patients with acquired immunodeficiency syndrome who develop this disease complication (12–15). In contrast to the situation with other disorders, no systematic guidelines have been formulated for PCP prophylaxis in the rheumatic diseases. A recent meta-analysis of clinical trials of PCP prophylaxis in non-HIV patients did not include a single trial of patients with autoimmune disorders (5,6).

In patients with rheumatic disease, many issues related to the prophylactic treatment for PCP have not been addressed adequately. Here we report 3 cases of PCP infection that occurred in patients with rheumatic disease after the discontinuation of cyclophosphamide (CYC) and high-dose glucocorticoids (Table 1).

**Case Report**

**Patient 1.** A 70-year-old woman with a history of Wegener’s granulomatosis (WG) was treated 3 years earlier with CYC and high-dose glucocorticoids. These medications were tapered off, but the patient subsequently developed pachymeningitis that required the reinstitution of immunosuppression. She resumed treatment with CYC (125 mg/day) and prednisone (60 mg/day). Because of a sulfa allergy, she was prescribed atovaquone (750 mg twice daily) as primary prophylaxis for PCP. Following 6 months of CYC therapy and a prednisone taper of 6 months’ duration, her disease was judged to be in clinical remission. The CYC, prednisone, and atovaquone were stopped. She was started on methotrexate (MTX; 20 mg/week) for remission maintenance.

Five months after starting MTX, the patient developed profound dyspnea on exertion and fever. Her oxygen saturation on room air was 78% (normal range 96–100%). A chest radiograph showed increased interstitial markings in both lower lobes (Figure 1). She was admitted to the intensive care unit (ICU), where MTX was discontinued because of concern for the possibility of MTX pneumonitis. Her total lymphocyte count was 158/\text{mm}^3 (normal range 1,100–4,800/\text{mm}^3). Bronchoscopy with bronchoalveolar lavage (BAL) revealed PCP organisms by staining and cytopathology. She was started on clindamycin (450 mg 4 times daily) and primaquine (15 mg of base/day). She narrowly avoided intubation and her clinical status remained tenuous for several days. Ultimately, the patient

---

1Anil Suryaprasad, MD: Johns Hopkins Bayview Medical Center, Baltimore, Maryland; 2John H. Stone, MD, MPH: Massachusetts General Hospital, Boston.
Address correspondence to John H. Stone, MD, MPH, Division of Rheumatology / Yawkey 2, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114. E-mail: jhstone@partners.org.
Submitted for publication October 21, 2007; accepted in revised form February 29, 2008.
was discharged in stable condition after a 3-week hospitalization. Her total lymphocyte count had increased to 1,260/mm³ at the time of her hospital discharge, and to 2,160/mm³ 2 months later. Four years after her PCP episode, the patient is not receiving any immunosuppressive therapy.

**Patient 2.** A 36-year-old woman presented with a malar rash, oral ulcers, autoimmune hemolytic anemia, thrombocytopenia, sicca symptoms, and pleuritis. She also had active urinary sediment and a serum creatinine level of 2.6 mg/dl (normal range 0.9–1.4 mg/dl). A diagnosis of systemic lupus erythematosus (SLE) was suspected, and a renal biopsy confirmed diffuse proliferative (global) lupus nephritis (16,17). She was treated with a 3-day pulse of methylprednisolone (1 gm/day) and also received 1 dose of intravenous CYC (500 mg/m²), with a plan to have her complete a full CYC course based on the regimen developed at the National Institutes of Health (18). As PCP prophylaxis, she began receiving trimethoprim/sulfamethoxazole (TMP/SMX; 1 double-strength tablet 3 times/week). Within 1 week, her renal dysfunction progressed to end-stage renal disease, and she began hemodialysis.

The patient tolerated CYC poorly. Over the next 10 weeks, she was hospitalized 3 times because of neutropenic fevers, central line infections, pulmonary infiltrates, and cholestatic jaundice. Her cholestasis was attributed to her TMP/SMX, which was discontinued. Because of G6PDH deficiency, she was prescribed atovaquone (750 mg twice daily) as PCP prophylaxis. The patient received a second administration of intravenous CYC during this period, but her course of CYC was discontinued permanently when her renal function showed no signs of recovery and she was rehospitalized for neutropenic fever, dyspnea, and bilateral lung infiltrates. Bronchoscopy with BAL at that time was negative for pathogens. The infiltrates cleared quickly and were attributed to fluid overload. Her prednisone was tapered to a dosage of 10 mg/day. The atovaquone was discontinued because she was no longer receiving CYC or high doses of glucocorticoids.

One month later, the patient developed fulminant respiratory failure characterized by bilateral alveolar infiltrates. She required intubation and mechanical ventilation. Her total lymphocyte count at that time was 160/mm³ (normal range 1,100–4,800/mm³). Repeat BAL revealed PCP (Figure 2). The PCP infection was treated with methylprednisolone (100 mg 3 times/day) and intravenous pentamidine (4 mg/kg every other day), but her respiratory status remained tenuous. Chest radiographs evolved into a pattern consistent with adult respiratory distress syndrome. After 2 weeks in the ICU, she underwent a tracheostomy.

---

**Table 1. Clinical data of 3 patients with autoimmune disease who developed PCP***

<table>
<thead>
<tr>
<th>Features of PCP cases</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disease</td>
<td>WG</td>
<td>SLE</td>
<td>WG</td>
</tr>
<tr>
<td>Lymphocyte nadir, per mm³</td>
<td>158</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>Immunosuppression at onset of PCP</td>
<td>None</td>
<td>Prednisone, 10 mg</td>
<td>None</td>
</tr>
<tr>
<td>Duration of immunosuppression, days</td>
<td>438</td>
<td>114</td>
<td>201</td>
</tr>
<tr>
<td>Primary PCP prophylaxis</td>
<td>Atovaquone (none for 5 months)</td>
<td>Atovaquone (none for 1 month)</td>
<td>Dapsone (patient noncompliant)</td>
</tr>
<tr>
<td>Hospital time course, days including ICU</td>
<td>14</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>Morbidity/mortality</td>
<td>Intubation</td>
<td>Intubation; tracheostomy; Clostridium difficile death</td>
<td>Intubation; Clostridium difficile death</td>
</tr>
<tr>
<td>Therapy</td>
<td>Clindamycin/primaquine</td>
<td>Dapsone and TMP due to pancytopenia</td>
<td>TMP/SMX after desensitization</td>
</tr>
<tr>
<td>Adverse events with prophylaxis</td>
<td>Nausea/vomiting; dyspnea; nonadherence</td>
<td>Rash (TMP/SMX); cholestasis; pancytopenia</td>
<td>Stevens-Johnson syndrome (TMP/SMX)</td>
</tr>
</tbody>
</table>

* PCP = Pneumocystis jiroveci pneumonia; WG = Wegener’s granulomatosis; SLE = systemic lupus erythematosus; ICU = intensive care unit; TMP = trimethoprim; SMX = sulfamethoxazole.

---

**Figure 1.** Chest radiograph from patient 1, showing bilateral interstitial infiltrates in the lower lobes caused by Pneumocystis jiroveci pneumonia infection.
Following 5 weeks in the ICU, her total lymphocyte count had increased to 3,373/mm³, but she remained ventilator dependent. During week 6, the patient died from an intracranial hemorrhage in the left frontal lobe. No autopsy was performed.

Patient 3. A 64-year-old man with WG developed rapidly progressive glomerulonephritis. His WG had been characterized previously by constitutional symptoms, nasal inflammation and crusting, migratory oligoarthritis, myalgia, and diffuse anterior scleritis. A renal biopsy revealed necrotizing, pauci-immune glomerulonephritis with crescents. The patient began urgent hemodialysis and was treated with CYC (150 mg/day) and prednisone (80 mg/day), followed by a glucocorticoid tapering regimen.

Five months later, while still receiving CYC at his original dose and prednisone (30 mg/day), the patient was judged to be in clinical remission. However, he had become profoundly leukopenic, with a white blood cell count of 2,200/mm³ despite a continuously high dose of prednisone. The patient’s CYC was stopped immediately, and he was started on a prednisone taper designed to discontinue that medication over the next 2 months. PCP prophylaxis was initiated as TMP/SMX (1 single-strength tablet daily), but the TMP/SMX was stopped after the patient developed a diffuse skin rash with mucous membrane involvement. After testing negative for G6PDH deficiency, the patient began dapsone (100 mg/day) as prophylaxis for PCP. Rheumatology consultants suggested that the CYC be stopped and that azathioprine (100 mg/day) be considered for remission maintenance once his white blood cell count had risen above 4,000/mm³.

Two months later, the patient was hospitalized for rapidly progressive hypoxic respiratory distress. At the time of his hospitalization, his total lymphocyte count was 0/mm³. A computed tomography scan of the chest revealed bilateral interstitial infiltrates (Figure 3). Although the initial suspicion of the clinicians was a WG flare, bronchoscopy and BAL revealed PCP organisms. The patient required a 58-day hospitalization, marked by a prolonged ICU course. He underwent desensitization to TMP/SMX and completed a course of that agent for his PCP. A followup lymphocyte count at the end of his hospital course was 500/mm³. Two years after his episode of PCP, he is not receiving any medications for his WG.

Discussion

PCP infections in patients with autoimmune disorders exact major tolls in morbidity and mortality (12–15). PCP in the autoimmune disease host typically presents abruptly, with advanced pulmonary compromise, a high risk of ICU admission and intubation, and a mortality rate documented to be between 30% and 60% (14,15). Although some cases of PCP in patients with rheumatic disease still reflect errors of omission, such as failure on the part of the clinician to implement prophylaxis, many others result from the wide knowledge gap that persists regarding PCP prophylaxis for patients with autoimmune disease.

This case series addresses the uncertainty regarding the appropriate time to discontinue prophylactic treatment after a course of intensive immunosuppression. The patients in this series shared a number of clinical features, including autoimmune diseases associated with systemic inflammation, immunosuppression with both CYC and high-dose glucocorticoids, persistence of CD4 lymphopenia after the discontinuation of immunosuppression, lapsed PCP prophylaxis, and the subsequent occurrence of life-threatening or fatal PCP.

There are 3 direct clinical implications of these cases. First, clinicians must be vigilant about prescribing prophylaxis for PCP and ensuring that it is maintained. This often requires perseverance, because clinicians can encounter one hurdle after another in the maintenance of PCP prophylaxis, e.g., allergic reactions or other adverse effects to the prophylactic agent (interstitial nephritis, Stevens-Johnson syndrome), patient noncompliance, and the cost of medications (Table 2). In addition, there is some concern among clinicians who treat patients with SLE that the administration of sulfa-based therapies can trigger a lupus flare (19).
The second implication is that clinicians should be cautious about the timing of discontinuing PCP prophylaxis, even after the period of intensive immunosuppression is over. The optimal duration of PCP prophylaxis among patients with autoimmune disease has not been investigated thoroughly. The appropriate duration is probably affected by such factors as the underlying disease, the particular agent(s) used to treat the autoimmune disorder, and the patient-specific factors that modify the metabolism of immunosuppressive drugs. Our 3 cases suggest that the need for PCP prophylaxis can extend for months beyond the time when patients are receiving intensive immunosuppressive therapy.

Finally, these cases underscore the importance of considering PCP prophylaxis in light of the patient’s underlying autoimmune condition and emphasize several issues for which there is little evidence-based guidance in the rheumatic diseases.

There is some evidence in the literature that a patient’s underlying disease affects the risk of PCP. For example, some reports suggest that patients with dermatomyositis are at a heightened risk for PCP (20–22). The basis of this increased risk, if true, is not clear. PCP has also been reported in a high percentage of patients with WG treated with intensive courses of CYC and glucocorticoids before the institution of PCP prophylaxis was incorporated as part of routine treatment (9). Although the occurrence of PCP has been reported in many other studies of patients with WG (23,24), the frequency of this complication may relate more to the intensive immunosuppression used in those series than to an inherent immune defect in WG.

In contrast to dermatomyositis and WG, the Scleroderma Lung Trial assigned patients with diffuse systemic sclerosis to either intravenous CYC plus glucocorticoids or glucocorticoids alone. PCP prophylaxis was not provided, yet among the total of 158 patients enrolled, not a single case of PCP was observed in either treatment group (25). Although some investigators view PCP as an unusual complication of SLE, patient 2 demonstrated that PCP infections can develop in patients with SLE, even when the patient is no longer receiving CYC and is receiving only low doses of prednisone. PCP complications of SLE therapy are also documented in the literature (25,27). In a review of PCP that complicated the courses of 34 patients with autoimmune conditions, 2 of the PCP cases occurred in patients with SLE who were receiving no immunosuppressive medications at the time of their infection (26). Clinicians need clearer guidance about which types of rheumatic disease merit consideration of PCP prophylaxis.

The few formal recommendations on which specific immunosuppressive regimens require PCP prophylaxis diverge from clinical reality. Some PCP experts recommend that any patient treated with “prolonged daily systemic corticosteroid therapy” should receive PCP prophylaxis (28). However, such recommendations generally specify neither what is meant by “prolonged,” nor the threshold of daily glucocorticoid dose that should trigger prophylaxis. One expert has proposed that PCP prophylaxis be used for all underlying immunologic disorders conferred by an inflammatory disease, chemotherapy, or organ transplantation, provided that the patient receives ≥20 mg of prednisone daily for >1 month (29,30). This recommendation reflects the consensus opinion of PCP experts that high-dose glucocorticoids comprise the major risk factor for this infection (14).

Within the rheumatic diseases, there are several prominent examples in which this proposal for prophylaxis is not incorporated into standard treatment. For example, treatment reviews of both giant cell arteritis and sarcoidosis do not suggest the routine use of PCP prophylaxis (31,32), despite the fact that prolonged glucocorticoid use is the backbone of treatment for these conditions. This neglect of PCP prophylaxis in giant cell arteritis and sarcoidosis may or may not be a legitimate concern. To our...
knowledge, there are few robust data about the risk of PCP in patients with either of these diseases. These discrepancies between expert recommendations and clinical practice in the rheumatic diseases illustrate the need for a more evidence-based approach on many issues.

In patients with rheumatic diseases, immunosuppressive medications other than glucocorticoids almost certainly contribute substantially to the risk of PCP. The challenge of providing recommendations for PCP prophylaxis in autoimmune conditions becomes murky when one considers combinations of immunosuppressive and immunomodulatory therapies. Patients with rheumatoid arthritis do not receive PCP prophylaxis routinely, even when they require the simultaneous use of low to moderate doses of prednisone, MTX, and a biologic agent. Yet in recent years, cases of PCP have been reported in patients receiving tumor necrosis factor α inhibitors (33).

Rheumatologists have not participated in the development of guidelines for PCP prophylactic treatment. In general, the literature on these issues has been written by infectious disease specialists, pulmonologists, oncologists, and transplant physicians. These investigators are experts in PCP and are experienced in caring for patients within their own subspecialties, but generally have limited training in the nuances of rheumatic disease. More importantly, few have direct experience with the kinds of immunosuppressive regimens prescribed longitudinally by rheumatologists.

Treatment with a course of CYC can lead to profound and lengthy depressions of the lymphocyte count. This fact, reported in the early 1970s (34), is not appreciated by many clinicians today. Between the 1970s and the present, few detailed studies using more recent lymphocyte markers have been performed in patients with rheumatic disease.

We note that in contrast to the situation with HIV disease, the correlation between CD4 counts and PCP risk is less clear in non-HIV disorders. For example, among 1,299 organ transplant patients, 28 developed PCP infections (35). The mean CD4 count in the group of patients infected was 281/mm³, indicating that many patients developed their PCP at CD4 counts well above the guideline for the termination of prophylaxis in patients with HIV. To our knowledge, comparable data do not exist in patients with rheumatic disease who have developed PCP. All 3 of our patients had profound lymphopenia, including CD4 lymphopenia.

In the absence of solid evidence about how long PCP prophylaxis should be maintained after the discontinuation or tapering of immunosuppressive drugs, we suggest that clinicians consider checking CD4 lymphocyte counts in patients for whom the discontinuation of PCP prophylaxis is considered. If the CD4 count is <200/mm³, clinicians should consider continuing prophylactic treatment until the counts are consistently above this level for 6 months. We acknowledge that because of the qualitative effect of immunosuppressive agents on lymphocyte function, this measure is unlikely to be a perfect surrogate for immunocompetence with regard to PCP, in contrast to the situation among patients with HIV (who are generally not receiving immunosuppressive medications). This proposal and other measures of immunocompetence require further study in prospective cohorts of patients with autoimmune disease.

In conclusion, many issues related to PCP prophylaxis in the rheumatic disease host differ from the approach to HIV disease, organ transplantation, and malignancy. The issue framed most clearly by the outcomes of these 3 patients is the appropriate duration of PCP prophylaxis following the tapering or cessation of immunosuppressive therapy. These and other questions related to PCP prophylaxis require careful clinical study and correlation with peripheral CD4 lymphocyte counts and other potential markers of immunosuppression.

REFERENCES


