Editorial


Is There a Role for Consensus Guidelines for *P. jiroveci* Pneumonia Prophylaxis in Immunosuppressed Patients with Rheumatic Diseases?

Pneumocystis jiroveci pneumonia (PCP) is the most common opportunistic infection in patients with human immunodeficiency virus (HIV)[1]. PCP can also affect patients with autoimmune diseases [e.g., systemic lupus erythematosus (SLE), Wegener's granulomatosis (WG), rheumatoid arthritis (RA), and inflammatory bowel disease] as well as hematological malignancies, organ transplants, and those receiving longterm immunosuppression. In the HIV population, the significant morbidity and mortality of PCP led to the development of specific guidelines for prevention, which has resulted in a dramatic reduction in the incidence of PCP. Similar guidelines for PCP prophylaxis have been developed for patients with organ transplants and undergoing cancer treatment[2,3].

The absolute incidence and need for chemoprophylaxis in patients with autoimmune diseases has not been well defined, and there are currently no consensus guidelines for PCP prophylaxis. This is due at least in part to a lack of clinical studies in patients with rheumatic diseases. The lack of consensus has led to significant differences in the use of PCP prophylaxis among rheumatologists, as highlighted in a study in this issue by Cettomai, *et al*[4].

The requirement for PCP prophylaxis is based on a risk-benefit assessment taking into consideration several important issues: (1) the incidence of PCP in the specific population (disease and/or immunosuppressive regimen); (2) the morbidity and/or mortality associated with PCP; and (3) the adverse effect profile of the chosen prophylactic regimen. Whether other key clinical and/or laboratory risk factors can help define who should receive PCP prophylaxis and whether the risk-benefit assessment falls in favor of prophylaxis has not been adequately addressed in patients with rheumatic diseases.

The Burden of PCP in Rheumatic Diseases

Infection risk in patients with connective tissue disease (CTD) is increased by the immune dysregulation associated with the disease itself, as well as the use of immunosuppressive therapies. It is difficult to distinguish between these factors in assessing risk of PCP in various conditions; however, cohort studies have consistently found PCP to be most common in patients with WG, although significant numbers of cases have been reported in patients with other conditions. In a metaanalysis of infection in 11,905 patients with connective tissue diseases, 12% of the 578 patients with WG developed PCP, compared with 6% of patients with dermatomyositis or polymyositis, 5% of SLE patients, and 1% of patients with RA[5].

Ward and Donald[6] used hospitalization registries to estimate frequencies of 89 cases of PCP per 10,000 hospitalizations in patients with WG; comparable figures for other conditions were 65 for polyarteritis nodosa, 27 for inflammatory myopathy, 12 SLE, 8 scleroderma, and 2 RA. PCP has been reported in patients with giant cell arteritis, but in small numbers.

The goal of remission in rheumatic diseases has led to widespread use of intensive immunosuppressive regimens. Commonly used immunosuppressive therapies have been associated with PCP including cyclophosphamide, methotrexate (MTX), corticosteroids, azathioprine, cyclosporine, and the newer biological agents including anti-tumor necrosis factor and anti-CD20 agents. Corticosteroids seem to be an important risk factor, with up to 90% of patients receiving corticosteroid therapy prior to development of PCP[7]. Cyclophosphamide can be associated with prolonged and significant reduction in lymphocyte counts; whether monitoring CD4+ lymphocyte counts should become routine clinical practice will be considered below. There is debate as to the extent of risk associated with MTX, but at least in RA the risk of infections is lower than has been thought in the past[8].

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Morbidity and Mortality Associated with PCP in Rheumatic Diseases

PCP in patients with rheumatic diseases is associated with significant morbidity and mortality. The need for intensive care admission and assisted ventilation is high. The overall mortality from PCP in HIV-negative patients is ~30%–60%, significantly higher than the reported 10%–20% mortality rate in HIV-positive patients[1,9]. The estimated mortality from PCP in patients with underlying rheumatic disease varies according to the condition; 62.5% in WG, 57.7% in inflammatory myopathy, 47.6% in polyarteritis nodosa, 30.8% in RA, and 16.7% in systemic sclerosis[6]. Given the higher mortality in HIV-negative patients it has been suggested that the threshold for commencing PCP chemoprophylaxis should be lower in this group of patients[10].

Other Clinical and Laboratory Risk Factors

In patients with HIV/AIDS the use of a cutoff CD4+ count of 200 cells/mm^3 is well established as an indicator for commencing PCP prophylaxis[11]. Although lymphopenia is present in almost all patients with connective tissue disease who develop PCP, exact levels are less definitive[10]. Lymphocyte and CD4+ counts in SLE patients 6–7 months before PCP onset were significantly lower than counts in age- and sex-matched SLE patients who did not develop PCP (CD4+ counts 156 vs 276/mm^3; $p = 0.01$) in one study[12], while Iikuni, *et al* found that RA patients who died from PCP had significantly lower CD4+ counts than those who survived (198.4/mm^3 vs 593.0/mm^3; $p < 0.05$), with drops in both lymphocyte count and IgG seen over the 6 months prior to illness[13].

Mansharamani, *et al*[14] suggested using a cutoff of < 300/mm^3 CD4+ cells for prophylaxis, which would include 91% of all HIV-negative patients with PCP. However, 39%–47% of patients on longterm corticosteroids had CD4+ counts below this level. Sowden and Carmichael[10] suggest instead measuring CD4+ counts after 1 month of immunosuppression in patients taking > 15 mg prednisolone daily (or equivalent), with > 3 months of treatment proposed, and a total lymphocyte count < 600 cells/mm^3. They recommend starting prophylaxis if the CD4+ count is below 200 cells/mm^3 and the annual risk of PCP is greater than 9%. Until prospective studies are conducted, however, it is impossible to know which strategy will be more effective in clinical practice.

Other methods for detecting high-risk patients may also have a part to play. Mori, *et al* found that 9 of 82 patients with RA were positive for *P. jiroveci* on polymerase chain reaction testing of induced sputum or bronchoalveolar lavage fluids; eradication of carriage without ongoing prophylaxis appeared to both prevent disease and prevent further colonization despite subsequent immunosuppression[15].

PCP Prophylactic Regimens

Trimethoprim-sulfamethoxazole (TMP) is the most commonly used prophylactic agent. While the direct benefit of TMP in preventing PCP is established in pediatric oncology patients[16] and patients with HIV[17], similar studies have not been undertaken in patients with rheumatic disorders. In patients with WG, TMP has been associated with the additional benefit of decreased disease relapse[18], but there is no evidence for a disease-modifying role in other conditions. Adverse effects associated with TMP occur in less than 20% of patients, most commonly pruritus, rash, leukopenia, elevation of transaminases, and nausea. Severe, life-threatening reactions including dermatologic and hepatotoxic reactions have been reported but are rare. MTX is the most commonly used disease-modifying agent in rheumatology. Hematopoietic suppression may occur when TMP and MTX are co-prescribed, although the combination has been used successfully with close monitoring of the blood count[19]. There is also some concern that sulfur-based medications such as TMP can trigger SLE or lupus flares.

Alternatives to TMP include oral dapsone or atovaquone, or nebulized pentamidine given monthly. However, these are considered second-line agents and may be limited by other factors such as cost (atovaquone) or need for hospital administration (pentamidine).

The duration of PCP prophylaxis in patients where disease activity and intensity of immunosuppression varies over time remains to be determined.

Summary

The lack of consensus guidelines for PCP prophylaxis in patients with rheumatic diseases reflects the lack of prospective and/or interventional studies in this area. However, studies have consistently shown PCP to occur in a significant minority (up to 12%) of such patients, especially those with WG, and disease mortality is also significantly higher in these and other HIV-negative patients. Disentangling the relative contributions of disease and treatment towards immunosuppression in this setting is difficult and may be unhelpful, as most of these patients are likely to need longterm immunosuppression. Cyclophosphamide treatment, however, appears to be associated with a particularly significant risk.

Research into the efficacy of prophylactic regimens in these patients would obviously be helpful, and should also consider other unanswered questions such as duration of prophylactic therapy and alternative regimens. Particularly high-risk patient groups may also be able to be identified on the basis of treatment (drug or dosage) or asymptomatic carriage of *P. jiroveci*. However, delaying action until these questions are answered may result in significant morbidity and mortality in high-risk groups of patients. In the absence of consensus guidelines, our current practice is to routinely provide PCP prophylaxis (usually oral TMP 3 times a week)

for all patients receiving cyclophosphamide and for patients with a history of PCP; usage in other patients is determined on a more individual basis, such as in those with persistent lymphopenia and CD4+ counts < 200 cells/mm^3. Efforts should be made to develop consensus guidelines while definitive evidence is awaited.

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