Editorial

Pneumocystis jirovecii Pneumonia Prophylaxis in non-HIV pulmonary patients on chronic corticosteroid therapy: make a virtue of necessity?

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Pneumocystis jirovecii pneumonia (PCP) was an uncommon disease before 1970, as it was recognized only scarcely in malnourished patients as well as in patients with hematologic malignancies and congenital immunodeficiencies. The onset of AIDS epidemic in the early 1980s was associated with a significant rise in its frequency and detection, so that PCP was considered the most common AIDS defining illness. The advent of organ transplantation and the development of new immunosuppressants further contributed to the expansion of PCP, so that nowadays the disease is an emerging issue among non-HIV pulmonary patients receiving chronic immunosuppression or having an underlying acquired or inherited immunodeficiency.[1,2] Corticosteroids (CS) appear to be the most commonly implicated agents in this regard, particularly when used in combination with other immunosuppressants, for the treatment of chronic lung disorders such as bronchial asthma, COPD, interstitial lung diseases, lung cancer, or systemic diseases (vasculitis, connective tissue disorders, immunodeficiencies) with pulmonary involvement.[3,4] This cohort of patients is often characterized, apart from a status of immunosuppression, by structural abnormalities of the lungs as well.[5] The morbidity and mortality of PCP is significantly worse in this population compared to patients who are HIV-positive.[6,7]

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii,* an atypical fungal microorganism that cannot grow outside its specific host, more precisely humans. *Pneumocystis* colonization occurs frequently in children and is more prevalent in the HIV-infected population. Also some groups of adult patients (other than HIV-infected) are at higher risk of *Pneumocystis* colonization such as patients with chronic lung diseases.[1,8,9] Individuals colonized with *Pneumocystis* may be at risk of development of PCP.[1,10,11]

In an infected host, *Pneumocystis* exists almost exclusively within the alveoli of the lung. The trophic forms attach to the alveolar epithelium. Alveolar macrophages are the primary resident phagocytes that mediate the clearance of the microorganisms from the lung. Once internalized, *Pneumocystis* is incorporated into phagolysosomes and subsequently degraded,

underlying the essential role of macrophages in the control of PCP.[12] Immune control of *Pneumocystis* also involves production of chemokines and inflammatory cytokines by alveolar macrophages and epithelial cells.[12] Ultimately, pattern recognition induces chemokines and inflammatory cytokine production, which promote neutrophils and T-lymphocyte recruitment and activation. $CD4^+$ T cells are essential for the control of *Pneumocystis* infection, as they coordinate the host inflammatory response by recruiting and activating additional immune effector cells including monocytes and macrophages, which are responsible for elimination of the organism. Low levels of $CD4^+$ T lymphocytes (<200/μl), therefore, disease or drug induced, may increase the risk of PCP.[1,13-15]

Corticosteroids inhibit not only the expression and action of many cytokines involved in the inflammatory response associated with pneumonia, but also inhibit a variety of inflammatory mediators. The consequence is that the local inflammatory response is markedly diminished in patients having received CS for large periods of time.[4] It is evident therefore, how the interplay between corticosteroid effects and impaired cell-mediated immunity increases the risk of development of PCP in this cohort of pulmonary patients.[16] Chronic lung disorders, age and smoking are recognized as independent factors of poor prognosis of PCP in patients without HIV infection.[17] Morbidity and mortality of PCP in non-HIV patients still remains high so that PCP prophylaxis for this group of patients should be of high priority in everyday clinical practice.[6,7]

Although, to our knowledge, no specific guidelines exist for PCP prophylaxis in patients with chronic lung disorders receiving long term high dose corticosteroids, the following recommendation recently published by The American Thoracic Society, may be considered for this specific cohort of patients:

- In immune-suppressed patients without HIV, prophylaxis should be considered during time periods where prednisone dose exceeds 20 mg/day for greater than 1 month, especially if the patient has associated T cell defects, or is receiving other cytotoxic drugs or anti-TNF agents.[18]

Moreover, a recent Cochrane review showed that prophylaxis for PCP using trimethoprim/sulfamethoxazole (TMP/SMX) is highly effective in patients with hematological malignancies, bone marrow transplantation and solid organ transplantation.[19] Data from this review and data available from studies conducted among HIV-positive patients revealed that TMP/SMX may be administered thrice weekly as the efficacy is similar to once daily administration. The adult dose of TMP/SMX most commonly administered in this review was 160/800 mg and the overall prevalence of adverse effects was low and did not result in treatment discontinuations.[19] In case of intolerance to TMX/SMX alternative options include atovaquone, dapsone, combination of dapsone with pyrimethamine and leucovorin, nebulized pentamidine.[19]

Quantitative incidence or relative risk data are lacking for patients with chronic lung disorders treated with corticosteroids for more than a month, in a dose equivalent to 20 mg of prednisone or more, that is considered to be a risk factor for the development of PCP.[3,19] Randomized control trials are needed for this large population of patients. Last but not least, the effect of prophylaxis on Pneumocystis resistance or on the development of resistant bacteria should be assessed in longitudinal studies or when TMP/SMX prophylaxis is used in practice.

COMPETING INTERESTS

All the authors declare that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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