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EDITORIAL

Primary and secondary prophylaxis for *Pneumocystis carinii* related complications in HIV patients

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At the beginning of the acquired immune deficiency syndrome (AIDS) era, nearly 15 yrs ago, *Pneumocystis carinii* pneumonia (PCP) was the most common human immunodeficiency virus (HIV)-related complication. PCP represented about 60% of the initial case-defining events of AIDS patients [1]. Almost 80% of HIV and AIDS patients experienced at least one episode of PCP in the course of their HIV infection [2, 3]. Thanks to secondary prophylaxis, the number of relapses of PCP has recently declined. But PCP is still the most commonly reported AIDS-associated diagnosis amongst HIV-infected individuals in Western industrialized countries [4]. Mortality was high, as the disease was not recognized early enough in many cases and the benefits of systemic steroids were not known at that point of time [5, 6].

Increased risks for PCP are: a CD4+ count <200 cells·μL^{-1} at the time of AIDS diagnosis; male homosexuality/bisexuality; and the diagnosis of AIDS in northern Europe [7]. Of AIDS patients with a history of one or more episodes of PCP, 60% are likely to experience another relapse within one year if specific prophylaxis is not administered [8, 9]. A recent study suggested that some recurrent episodes of PCP are caused by reinfection rather than by reactivation of latent infection. This hypothesis is based on genetic heterogeneity of mitochondrial ribosomal ribonucleic acid (RNA) gene of *Pneumocystis carinii hominis* isolates from AIDS patients with recurrent episodes of PCP [10].

In 1990, LEOUNG *et al*. [9] published the first report proving the prophylactic efficacy of inhaled aerosolized pentamidine against PCP in 408 high-risk HIV patients. A dose of 300 mg aerosolized pentamidine administered once monthly by jet nebulizer was the most effective secondary prophylaxis. After 18 months, only 8 out of 139 participants receiving the 300 mg schedule had experienced a PCP relapse, as compared with 22 out of 135 subjects having been randomized to receive the low dose of 30 mg pentamidine every 2 weeks [9]. Another study investigated the preventive value of inhaled pentamidine in 223 HIV patients (<200 CD4+ cells·μL^{-1}) or AIDS related complex = Centers for Disease Control (CDC) B3 in the current classification) without previous episode of PCP. Eight patients with primary prophylaxis *versus* 23 patients in the placebo group experienced a PCP (p=0.0021) [11].

On the basis of these two studies, the regular application of aerosolized pentamidine for primary and secondary prophylaxis against PCP had become a standard of management in HIV patients with less than 200 CD4+ cells·μL^{-1} or in AIDS patients with a previous episode of PCP.

Administration of pentamidine by jet nebulizer and by ultrasonic nebulizer provides sufficient respirable particles [12]. Adverse events are rare and limited to transient unpleasant taste and cough. Smokers or patients with bronchial hyperreactivity may develop bronchospasm, which is usually prevented by prior administration of two puffs of a bronchodilator [13]. Long-term, unwanted effects or irreversible ventilatory dysfunctions are not known in patients regularly inhaling aerosolized pentamidine [14, 15]. Rash [16], pancreatitis [17], hypoglycaemia [17], diabetes [18], and renal insufficiency [19] have been described but occur much more commonly when pentamidine is administered intravenously. The association between the application of aerosolized pentamidine and the development of spontaneous pneumothorax is well-known [20]. Also, the financial aspects of aerosolized pentamidine cannot be overlooked; this prophylaxis being about five times more expensive than the administration of co-trimoxazole and about 10 times as expensive as dapsone.

Additionally, there have been several reports describing extrapulmonary manifestations of *Pneumocystis carinii*. These are found in 0.5–3% of patients with PCP [21]. About 50% occur in HIV patients, despite regular inhalation of aerosolized pentamidine. Positive blood polymerase chain reactions (PCRs) for *Pneumocystis carinii* indicate haematogenous spread during acute pneumonia [22]. Almost all organs can be involved in disseminated *Pneumocystis carinii* infections in AIDS. Examples are mastoiditis [23], skin manifestations [24], hepatitis [25], splenitis [26], thyroiditis or the involvement of the bone marrow [27] with secondary pancytopenia.

In this issue of the Journal, EWIG *et al*. [28] report an incidence of breakthrough PCP of 23% at 36 months in 95 HIV-infected patients with primary aerosolized pentamidine prophylaxis, similar to results published previously [29]. EWIG *et al*. [28] compared the clinical and radiographic presentation as well as the outcome of breakthrough PCP in those patients with "early" (≤12 months of inhalation time) and with "late" (>12 months of inhalation time) failure, and found no difference between these two groups. Presentation with upper lobe infections was also a radiographic pattern of late failures. EDELSTEIN and MCCABE [30] first described this atypical presentation in 1990 and, in contrast to EWIG *et al*. [28], they observed complicated courses, such as cavities and pneumothoraces. Lung cavitation in PCP may also occur without inhaled pentamidine prophylaxis [31].

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One limitation of the report by EWIG *et al*. [28] is the small number of breakthrough PCP, which makes the statistical comparison of the two populations doubtful (six cases of "early" failure *versus* 14 cases of "late" failure). Like others before, EWIG *et al*. [28] advise the site-directed lavage technique [32]. This recommendation is particularly important to enhance the diagnostic sensitivity in cases of PCP with atypical clinical and/or radiographic presentation. Some clinicians recommend that aerosolized pentamidine should be inhaled in different positions (sitting as well as lying), believing that this ensures better contact of the upper pulmonary lobes with the aerosol. No published data are available to confirm the efficacy of this procedure. It is important to note that systemic prophylaxis with trimethoprim-sulphamethoxazole (TMP-SMX) is also associated with upper lobe recurrence of PCP [33].

The limitations of an effective prophylaxis against systemic pneumocystosis with inhaled pentamidine and the incomplete protection for patients with a history of prior PCP have been important reasons to search for alternative prophylactic regimens.

The introduction of orally administered TMP-SMX solved some of the problems discussed above. TMP-SMX is inexpensive, can be administered orally and provides a systemic distribution of the agent. The first controlled trial comparing the efficacy of TMP-SMX with aerosolized pentamidine in secondary prophylaxis of PCP in 310 AIDS patients showed that TMP-SMX is superior to aerosolized pentamidine with respect to the recurrences of PCP (14 *versus* 36 relapses; $p<0.001$) [34]. Moreover, bacterial infections and cerebral toxoplasmosis occurred less often during therapy with TMP-SMX. Similar results were obtained in a trial for primary prophylaxis [35]. Consequently, in 1992 the US Public Health Service recommended TMP-SMX as first-line prophylaxis for all HIV-infected patients at high risk for acquiring PCP [36]. Different regimens were tested to define the minimal dose of TMP-SMX necessary to prevent PCP and toxoplasmosis. Trimethoprim, 160 mg, and sulphamethoxazole, 800 mg, (= one double-strength tablet three times a week [37], or two double-strength tablets two times a week [38]) yield comparable satisfying results.

Dapsone is another promising antifolate drug for *Pneumocystis carinii* and *Toxoplasma gondii* prophylaxis. Oral dapsone, 100 mg, has been shown to be as effective as the daily intake of one double-strength tablet of TMP-SMX in primary PCP prophylaxis [39]. However, dapsone is associated with haemolytic anaemia and methaemoglobinaemia in rare cases. A recent study compared the oral administration of 200 mg dapsone together with 75 mg pyrimethamine once a week with aerosolized pentamidine. The randomized, open trial demonstrated a longer survival time in the pentamidine group [40]. However dapsone/pyrimethamine more effectively prevented infections with *Pneumocystis carinii* and *Toxoplasma gondii* than aerosolized pentamidine [41]. Moreover, a subanalysis of the results of this study reveals a slight, non-significant trend indicating that this regimen may provide an additional prophylactic effect against atypical mycobacterial infections [42].

A number of studies in 1993 have already suggested the superior effect of dapsone/pyrimethamine over aerosolized pentamidine for the simultaneous prevention of cerebral toxoplasmosis. These studies have shown an at least equal effect of dapsone/pyrimethamine on primary PCP prophylaxis compared with aerosolized pentamidine [43, 44]. PODZAMCZER *et al*. [45] demonstrated that thrice weekly TMP-SMX was even more effective than weekly dapsone-pyrimethamine for the primary prevention of PCP in HIV-infected patients. In contrast, a large study (n=843) published in 1995 showed a similar efficacy of TMP-SMX and dapsone, with an estimated 36 month cumulative risk of 19 *versus* 22%, respectively [28]. Both were superior to aerosolized pentamidine (33% risk), especially in HIV patients with less than 100 CD4+ cells·μL^{-1}. The investigation consisted of three arms: TMP-SMX (one double-strength tablet *b.i.d.*) *versus* dapsone (100 mg *q.d.* orally) *versus* aerosolized pentamidine (300 mg every 4 weeks, administered by a Respigard II nebulizer). The median survival was approximately equal in all three groups and not related to new episodes of PCP [28].

In summary, many studies and a bulk of data exist dealing with the question of optimal primary and secondary prophylaxis against PCP/toxoplasmosis. As the investigators used different dosages of the same agent, enrolled differently immunocompromised populations of HIV patients, and investigated primary and secondary prophylaxis, it is difficult to obtain a clear picture of the optimal prophylactic regimen. In general, there are advantages of orally given drugs over aerosolized pentamidine, and TMP-SMX seems to be slightly superior to dapsone/pyrimethamine. However, aerosolized pentamidine remains an important reserve drug for PCP prophylaxis because some HIV patients are intolerant of antifolate agents and develop allergic reactions [34]. The simultaneous intake of folinic acid does not improve the tolerance to TMP-SMX whether zidovudine is additionally administered or not [46]. The consequent application of secondary PCP prophylaxis and the recent introduction of antiretroviral agents have increased the 1 and 2 year survival rates after the diagnosis of PCP.

However, 3 year survival has remained unchanged over time, implying that the underlying immunodeficiency and related infectious and malignant complications are not under control [47].

In conclusion, trimethoprim-sulphamethoxazole appears to be the treatment of choice for primary and secondary *Pneumocystis carinii* pneumonia prophylaxis. However, there is an urgent need for the development of new, better drugs with a wider range of protection against the various opportunistic infections.

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