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Pneumocystis jirovecii pneumonia in Spanish HIV-infected patients in the combined antiretroviral therapy era: prevalence of dihydropteroate synthase mutations and prognostic factors of mortality☆

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Abstract

The incidence of *Pneumocystis jirovecii* pneumonia (PCP) in HIV-infected patients has decreased thanks to sulfa prophylaxis and combined antiretroviral therapy. The influence of *P. jirovecii* dihydropteroate synthase (DHPS) gene mutations on survival is controversial and has not been reported in Spain. This prospective multicenter study enrolled 207 HIV-infected patients with PCP from 2000 to 2004. Molecular genotyping was performed on stored specimens. Risk factors for intensive care unit (ICU) admission and mortality were identified

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using a logistic regression model. Seven patients (3.7%; 95% confidence interval [CI], 1.5–7.5%) had DHPS mutations. Overall mortality was 15% (95% CI, 10–21%), rising to 80% (95% CI, 61–92%) in patients requiring mechanical ventilation. None of the patients with DHPS mutants died, nor did they need ICU admission or mechanical ventilation. PaO_2 <60 mm Hg at admission was a predictor of ICU admission ($P = 0.01$), and previous antiretroviral therapy predicted non-ICU admission ($P = 0.009$). PaO_2 <60 mm Hg at admission and ICU admission during the 1st week were predictors of mortality ($P = 0.03$ and $P < 0.001$, respectively). The prevalence of DHPS mutants in Spain is low and is not associated with a worse outcome. Severe respiratory failure at admission is the strongest predictor of PCP outcome.

Keywords: *Pneumocystis* pneumonia; DHPS mutations; HIV infection; cART; Outcome

1. Introduction

The morbidity and mortality of *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia (PCP) in HIV-infected patients has changed because of the systematic use of sulfa prophylaxis, adjunctive steroids in the acute episodes, and combined antiretroviral therapy (cART) (Huang, 2005). The incidence of PCP in Spain has decreased over the last 2 decades (Benito et al., 2001; San-Andrés et al., 2003) from 20 cases per 100 exposed patients/year in 1987, when sulfa prophylaxis was introduced, to 10 cases per 100 exposed patients/year in 1996, when cART was started. It currently stands at 0.1 cases per 100 exposed patients/year (Benito et al., 2001; San-Andrés et al., 2003). Nevertheless, PCP is still the 2nd most common HIV-related illness in Spain (21.7%) after tuberculosis (Boletín Epidemiológico Semanal [BES], 2005). In the early 1990s, mortality due to PCP was 28% (Fernández et al., 1995), rising to 40% in intensive care unit (ICU) patients and to 79% in patients who required mechanical ventilation (Alvés et al., 2001; Fernández et al., 1995).

The factors affecting mortality rates of PCP in HIV-infected patients during the cART era have been analyzed in the literature. Several studies have evaluated the influence of cART and sulfa prophylaxis on the outcome of PCP. A study found that cART improved survival in HIV-infected patients with severe PCP (Morris et al., 2003). However, another study showed that the improved survival for HIV-infected patients with severe PCP was independent of cART and reflected general improvements in ICU management of respiratory failure rather than improvements in the management of PCP (Miller et al., 2006).

Published studies worldwide have reported the presence of mutations in the *P. jirovecii* dihydropteroate synthase (DHPS) gene (Table 1) (Beard et al., 2000; Costa et al., 2003; Diop Santos et al., 1999; Esteves et al., 2008; Helweg-Larsen et al., 1999; Huang et al., 2000; Kazanjian et al., 1998, 2000, 2004; Latouche et al., 2003; Ma et al., 2002; Miller et al., 2003; Montes-Cano et al., 2004; Nahimana et al., 2003; Takahashi et al., 2000; Valerio et al., 2007; Visconti et al., 2001; Wissmann et al., 2006; Zar et al., 2004), although the role of DHPS mutations in response to treatment and outcome is controversial. These mutations, which are found on the sulfa binding site, are associated with sulfa prophylaxis failure (Armstrong et al., 2000; Beard et al., 2000; Kazanjian et al., 1998; Lane et al., 1997; Ma et al., 1999; Mei et al., 1998). However, although 3 studies found that they were associated with poor treatment outcome (Helweg-Larsen et al., 1999; Kazanjian et al., 2000; Valerio et al., 2007), the 4th did not (Navin et al., 2001). Recently, it has been found that the outcome and mortality of HIV-associated pneumonia containing *P. jirovecii* DHPS mutations are related to the underlying severity of illness and the initial severity of PCP more than to the presence of mutations (Crothers et al., 2005).

The impact of *P. jirovecii* DHPS gene mutations on the outcome of PCP in Spanish HIV-infected patients has not been reported. Accordingly, this study was undertaken i) to document the prevalence of *P. jirovecii* DHPS mutations in Spanish HIV-infected patients with PCP during the cART era, ii) to describe the influence of the mutations on the outcome and survival of these patients, and iii) to analyze mortality rates in HIV-infected patients with PCP during the cART era in Spain and identify the prognostic factors associated with poor outcome determined by ICU admission or death.

2. Materials and methods

A prospective multicenter study including 207 consecutive HIV-infected patients with PCP from 12 Spanish hospitals (Hospital Clínic [57 patients], Hospital Santa Creu i Sant Pau [22], Hospital Vall d'Hebrón [17], Hospital de Bellvitge [19], Hospital Germans Trias i Pujol [35], Hospital Parc Taulí de Sabadell [5], Barcelona; Hospital Joan XXIII [5], Tarragona; Hospital Son Dureta [17] and Hospital Son Llatzer [1], Mallorca; Hospital de Donostia [13], San Sebastian; Hospital Virgen del Rocío [15], Seville; and Hospital La Paz [1], Madrid) was performed between January 2000 and April 2004. Seven centers were in the northeast (Catalonia), 2 in the east (Mallorca), 1 in the north (San Sebastian), 1 in the center (Madrid), and another in the south (Seville). PCP infection was confirmed microscopically by bronchoalveolar lavage (BAL) or induced sputum (IS) as part of routine diagnostic procedures by local hospital microbiology or pathology departments. Frozen aliquots or alcohol-fixed slides of the clinical specimens were sent to the University of North Carolina (UNC, Chapel Hill, NC)