Article

Thrice-Weekly Sulfadiazine-Pyrimethamine for Maintenance Therapy of Toxoplasmic Encephalitis in HIV-Infected Patients


Abstract An open, randomised, multicentre trial was conducted to evaluate the efficacy of thrice-weekly versus daily therapy with sulfadiazine-pyrimethamine in the prevention of relapses of toxoplasmic encephalitis in HIV-infected patients. Between February 1994 and July 1997, 124 patients with HIV infection were enrolled after resolution of the first acute episode of toxoplasmic encephalitis treated with sulfadiazine-pyrimethamine. Patients were randomly assigned to receive either a daily regimen consisting of sulfadiazine (1 g) twice a day plus 25 mg pyrimethamine and 15 mg folinic acid daily (n = 58), or a thrice-weekly regimen consisting of the same doses of sulfadiazine and folinic acid plus 50 mg pyrimethamine (n = 66). After a median follow-up period of 11 months (range 1–39 months), no differences were found in the incidence of toxoplasmic encephalitis relapses between the groups, there being 14.9 episodes per 100 patient-years (95% CI: 2.8–20.2) in the daily-regimen group versus 14.1 episodes (95% CI: 2.3–17.2) in the intermittent-regimen group. The estimated cumulative percentages of relapse at 12 months were 17% and 19%, respectively (P = 0.91). In a Cox multivariate analysis, not taking antiretroviral therapy was the only variable independently associated with relapse (adjusted risk ratio: 4.08; 95% CI: 1.32–12.66). Baseline CD4+ cell counts, prior AIDS, mental status, sequelae and allocated maintenance therapy regimen were not independent predictors of relapse. No differences were observed in the survival rate (P = 0.42), or in the incidence of severe adverse effects (P = 0.79). The efficacy of the thrice-weekly regimen was similar to that of the daily regimen in the prevention of relapses of toxoplasmic encephalitis. Administration of antiretroviral therapy was the only factor associated with a lower incidence of relapse.
Introduction

Lifelong maintenance therapy of several opportunistic infections has been a major strategy in the management of HIV-infected patients since the early stages of the AIDS epidemic [1]. The frequency of relapse of infections such as *Pneumocystis carinii* pneumonia, toxoplasmic encephalitis or cryptococcosis has been dramatically reduced by some of the regimens used [1–4]. However, the need to consume a high number of tablets in regimens for antiretroviral therapy in addition to regimens for primary prophylaxis or maintenance therapy of opportunistic infections, renders compliance difficult and has negative effects on the patients’ quality of life. Intermittent regimens for primary prophylaxis or maintenance therapy of opportunistic infections may be as effective as, better tolerated than and more convenient than daily regimens [5, 6].

There has been a considerable decrease in the incidence of toxoplasmic encephalitis due to widespread use of cotrimoxazole for simultaneous primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmosis and, more recently, due to the use of highly active antiretroviral therapy (HAART). Nevertheless, toxoplasmic encephalitis continues to be a problem in a considerable number of severely immunosuppressed HIV-infected patients, especially in areas with a high prevalence of latent infection [7]. Moreover, despite the current use of HAART in many patients, the immunological defences are not sufficient on their own to prevent the development of toxoplasmic encephalitis or relapses after treatment of acute episodes.

The daily regimen most commonly used for maintenance therapy of toxoplasmic encephalitis consists of a combination of 500 mg sulfadiazine q.i.d. plus 25 mg pyrimethamine and 15 mg folinic acid daily, which amounts to 42 tablets weekly [3]. In a previously published study, a twice-weekly regimen was shown to be less effective than the daily regimen in preventing toxoplasmic encephalitis relapses [8]. In this study we evaluated the efficacy of a thrice-weekly regimen versus the daily regimen in the prevention of relapses of toxoplasmic encephalitis.

**Patients and Methods**

**Study Design.** This open, multicentre, randomised study was performed in Spain between February 1994 and July 1997 at 12 university teaching hospitals in Barcelona, Madrid, Santander, Palma de Mallorca and San Sebastian. HIV-infected patients were enrolled after resolution of an acute episode of toxoplasmic encephalitis treated with sulfadiazine (1 g q.i.d.) plus pyrimethamine (50 mg daily) and folinic acid (15 mg daily) for 4–8 weeks. Resolution was defined as a greater than 50% reduction in, or disappearance of, brain lesions on computed tomography (CT) or magnetic nuclear resonance imaging (MRI), and improvement or disappearance of clinical signs (fever, neurological findings, or both).

The administration of drugs with antitoxoplasma activity such as cotrimoxazole, clindamycin, clarithromycin, azithromycin or atovaquone for more than 10 consecutive days was not permitted during the study period. In order to evaluate the usefulness of the intermittent regimen in preventing a first episode of *Pneumocystis carinii* pneumonia, participating physicians were advised to avoid the use of inhaled pentamidine during the study period, but it was not forbidden (14 patients received 300 mg of inhaled pentamidine monthly). No other drugs with activity against *Pneumocystis carinii* were given during the follow-up period.

Patients were randomly assigned to receive either sulfadiazine (1 g b.i.d.) plus 25 mg pyrimethamine and 15 mg folinic acid daily, or the same doses of sulfadiazine and folinic acid plus 50 mg pyrimethamine thrice weekly. We decided to double the dose of pyrimethamine in the intermittent-therapy group due to the lower than expected efficacy of a low-dose intermittent regimen observed in our previous trial [8]. Randomisation was done in a central location using a random number table. The study was approved by local ethics committees and informed consent was obtained from patients.

Clinical and laboratory evaluations were done every 30–60 days. Parameters measured at baseline and during follow-up were blood cell counts, CD4+ cell counts, alanine aminotransferase levels, alkaline phosphatase levels and creatinine levels. At every examination compliance and any signs or symptoms of toxicity were evaluated, a physical examination was performed, and blood samples were obtained for blood cell counts and biochemical tests. The frequency with which CD4+ cell counts were performed during follow-up was determined by the treating physician. Brain imaging (CT or MRI) was only performed during follow-up in patients with signs and symptoms suggestive of toxoplasmic encephalitis relapse.

Primary end-points of the study were toxoplasmic encephalitis relapse, death, and interruption of therapy due to adverse effects. Development of *Pneumocystis carinii* pneumonia was a secondary end-point.

A probable toxoplasmic encephalitis relapse was diagnosed on the basis of clinical findings (fever, neurological signs and symptoms, or both); findings on one or more contrast-enhanced focal CT or MRI brain image or both; and response to sulfadiazine-pyrimethamine or clindamycin-pyrimethamine therapy. A possible toxoplasmic encephalitis relapse was diagnosed on the basis of clinical and imaging findings in the absence of an adequate response to specific therapy due to early death or other causes. Clinical and radiographic findings suggestive of *Pneumocystis carinii* pneumonia (preferably with microbiological confirmation) were required for diagnosis of this infection.

Two independent, blinded investigators evaluated the clinical records, the CT and MRI images, and the therapeutic response of persons initially diagnosed as having toxoplasmic encephalitis.

**Statistical Analysis.** Baseline characteristics were compared using Student’s *t* test (quantitative variables), or the chi-square or Fisher’s exact test when necessary (qualitative variables).

Efficacy was evaluated by intent-to-treat analysis, 124 of the 129 initially randomised patients being eligible for the analysis. These 124 patients were included in the analysis according to the regimen to which they had initially been assigned, and they were followed up until the end of the study even if the initially allocated treatment regimen was changed or stopped.

On the basis of our previous findings [8], it was assumed that the daily regimen would be equivalent or superior to the thrice-