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Article

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

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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.

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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-

weekly regimen in efficacy. It was calculated that 59 patients per group would be needed to detect a 15% difference in relapse rate with 80% statistical power and a 5% (one-tailed) significance level (calculated from an expected 5% probability of relapse in the daily-regimen group and 20% in the intermittent-regimen group). From a clinical standpoint smaller differences were not considered to justify the additional tablet burden or potential toxicity of a daily maintenance regimen.

If a two-tailed analysis had been done, a difference of 15% with 60% statistical power, or a difference of 20% with 80% statistical power would have been detected if it had existed. On the basis of our previous data [8], an interim analysis was planned after the occurrence of the first 15 episodes of toxoplasmic encephalitis relapse. The DSMB recommended interruption of the study since the toxoplasmic encephalitis relapse rates in both groups were similar (14.9 vs. 14.1 per 100 patient-years), and the sample size required for a 1% difference between regimens to be significant would be at least 14392 patients per study group with 80% statistical power and a 5% significance level (Sample 3.2 MRC Cancer Trial Office, Cambridge, 1993).

Relapse and survival rates were estimated by life-table analysis and compared using the log-rank test. The adjusted risk ratio and its 95% confidence intervals were calculated using the Cox multivariate proportional hazards regression method.

Covariates used in univariate and multivariate analysis were age (30 years), sex, HIV risk practices, previous diagnosis of AIDS, *Pneumocystis carinii* pneumonia prophylaxis administered before the initial episode of toxoplasmic encephalitis, antiretroviral therapy administered before the initial episode of toxoplasmic encephalitis, CD4+ cell counts (50 cells/μl), mental status (normal vs. abnormal), brain oedema, mass effect, number of lesions, persistence of contrast enhancement after an acute episode of toxoplasmic encephalitis, clinical and/or radiological sequelae, type of maintenance therapy, and antiretroviral therapy during follow-up. All these calculations were done using the SPSS 6.0 programme (SPSS, USA). A significance level of <0.05 was required in all cases.

The relapse risk per 100 patient-years and the 95% confidence intervals (Poisson distribution) were calculated using the STATA 5.0 program (Statacorp, USA).

Results

Patients. Five of the 129 patients initially recruited were randomised by error and considered not eligible for analysis. Their baseline diagnoses were progressive multifocal leukoencephalopathy in three cases, and central nervous system lymphoma and a second episode of toxoplasmic encephalitis in one case each. Four of these patients had been assigned to receive the daily regimen and one to receive the intermittent regimen. Thus 124 patients were included in the study: 58 patients received the daily regimen and 66 the intermittent regimen.

The baseline characteristics of the patients are listed in Table 1. No statistical differences were found in age, sex, risk practice, previous diagnosis of AIDS, CD4+ cell counts, *Pneumocystis carinii* pneumonia prophylaxis or antiretroviral therapy administered before the initial episode of toxoplasmic encephalitis, or neurological findings at the onset of the acute episode of toxoplasmosis (mental status, mean number of lesions, brain oedema, mass effect) or after the acute episode of toxoplasmosis (persistence of contrast enhancement, and clinical and/or radiological sequelae).

Efficacy and Toxicity. Sixteen patients experienced a relapse of toxoplasmic encephalitis (classified in 13 as a probable episode and in 3 as a possible episode) after a median follow-up period of 11 months (range 1–39 months). No differences in the number of episodes per 100 patient-years were observed between groups on intent-to-treat analysis, there being 14.9 episodes (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 (Table 2). The estimated cumulative percentages

Table 1 Baseline characteristics of 124 patients according to maintenance therapy regimen

Characteristic	Daily regimen ($n=58$)	Thrice-weekly regimen ($n=66$)	*P* value
Age in years	35.7	34.9	0.58
Male/female ratio	3.5	5.0	0.41
Risk behaviour			
Drug abuse	39 (67.2%)	45 (68.1%)	0.95
Homosexuality	10 (17.2%)	12 (18.1%)	
Other	9 (15.5%)	9 (13.6%)	
Prior AIDS	29 (51.7%)	33 (50.0%)	0.30
CD4+ cell counts (per μl)	48.3 ± 49.9	42.3 ± 49.6	0.51
PCP prophylaxis	32 (55.1%)	32 (48.4%)	0.45
Antiretroviral therapy[a]	21 (36.8%)	33 (50.7%)	0.30
Neurological signs			
Abnormal mental status	23 (41.0%)	27 (41.5%)	0.77
Mean number of lesions	2.4 (1– >6)	2.4 (1– >6)	0.90
Brain oedema	39 (69.6%)	49 (76.5%)	0.68
Mass effect	35 (62.5%)	40 (62.5%)	0.99
Persistence of contrast enhancement[b]	2 (3.5%)	6 (9.2%)	0.20
Clinical and/or radiological sequelae[b]	27 (46.5%)	29 (43.9%)	0.77

[a] Thirty (53.5%) and 43 (67.1%) patients received antiretroviral therapy during follow-up, respectively ($P=0.31$)
[b] After acute toxoplasmic encephalitis episode
PCP, *Pneumocystis carinii* pneumonia

Table 2 Outcome in 124 patients on sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis (TE)

Outcome	Daily regimen ($n=58$)	Thrice-weekly regimen ($n=66$)	Total
TE relapse			
No. of cases	7 (12%)	9 (13.6%)	16 (13%)
Incidence[a]	14.9 (2.8–20.2)	14.1 (2.3–17.2)	
Death	25 (43%)	28 (42.4%)	53 (43%)
Discontinued therapy	14 (24%)	13 (19.6%)	27 (22%)
Severe adverse effects	7 (12%)	7 (10.6%)	14 (11%)
Lost to follow-up	7 (12%)	6 (9%)	13 (10%)
Alive and still on therapy	12 (20.6%)	16 (24.2%)	28 (22.6%)

[a] Number of episodes per 100 patient-years (95% confidence interval); $P=0.41$; adjusted risk ratio 1.31 (95% CI: 0.47–3.65)

of relapse at 12 months were 17% and 19%, respectively, and at 24 months 30% and 19% respectively (log-rank, $P=0.91$; Figure 1). The results of the analysis, including the five patients randomised by error, were almost identical (data not shown).

Many patients who relapsed demonstrated poor compliance as follows: five of seven on the daily regimen, and three of nine on the intermittent regimen considering all relapses, and three of five and five of eight, respectively, considering only probable relapses.

No differences were observed between groups in the proportion of patients who continued the study during 1997 and received protease inhibitors as part of their antiretroviral regimens, the figures being 20 of 27 (74%) on the daily regimen and 19 of 33 (57.5%) on the intermittent regimen. In addition, no differences were found in the proportion of patients in whom CD4+ cell counts rose above 100 cells/μl (11/20 vs. 11/19) or above 200 cells/μl (6/20 vs. 6/19). Three patients experienced a toxoplasmic encephalitis relapse during 1997, only one of whom was receiving protease inhibitors and none of whom had CD4+ cell counts above 100 cells/μl.

No patient experienced a confirmed episode of *Pneumocystis carinii* pneumonia during follow-up. *Pneumocystis carinii* pneumonia was suspected on clinical grounds in four patients on the intermittent regimen: two patients responded to cotrimoxazole therapy while two did not respond and died.

Seven patients in each group discontinued therapy due to adverse effects (Table 2): five due to skin rash and/or fever and two due to gastrointestinal disturbances in the daily-regimen group, and five due to skin rash and/or fever and two due to haematological toxicity in the intermittent-regimen group ($P=0.79$).

Overall, 53 patients died during the follow-up period. No statistical differences in the survival rate were observed between groups. The median survival time was 588 days (95% CI: 424–751) in patients on the daily regimen, and 582 days (95% CI: 301–862) in patients on the intermittent regimen (log-rank, $P=0.42$).

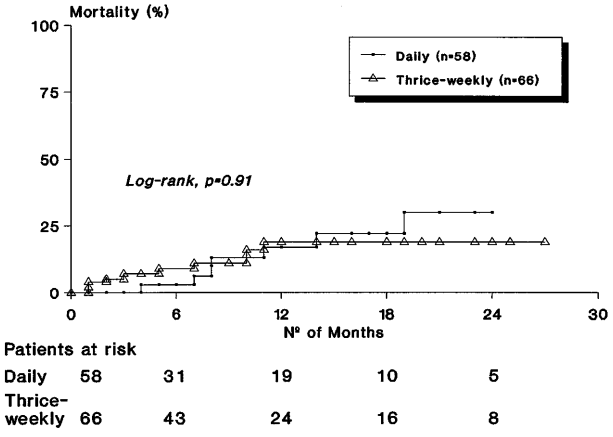

Figure 1 Kaplan-Meier plots of time to relapse of toxoplasmic encephalitis in HIV-infected patients

In a multivariate model, not receiving antiretroviral therapy during follow-up was the only variable independently associated with toxoplasmic encephalitis relapse (risk ratio: 4.08; 95% CI: 1.32–12.66), while prior AIDS, CD4+ cell counts, mental status, clinical and/or radiological sequelae, and type of maintenance regimen were variables not associated with relapse (Table 3).

Neither these variables nor other variables (age, sex, risk practice, *Pneumocystis carinii* pneumonia prophylaxis regimen and antiretroviral therapy administered before the toxoplasmic encephalitis episode, brain oedema, number of lesions, persistence of contrast enhancement after an acute episode of toxoplasmosis) were significantly associated with a higher risk of toxoplasmic encephalitis relapse (data not shown).

Discussion

Several years ago, multiple drug regimens for primary prophylaxis and maintenance therapy of opportunistic

Table 3 Multivariate analysis of factors related to toxoplasmic encephalitis relapse (Cox proportional hazards regression model)

Variable	Risk ratio	95% CI
Normal mental status	0.96	0.34–2.62
No prior AIDS	0.82	0.30–2.25
Sequelae[a]	1.15	0.41–3.26
Thrice-weekly group	1.31	0.47–3.65
No antiretroviral therapy[b]	4.08	1.32–12.66
CD4+ count >50/μl at baseline	0.42	0.09–1.95

[a] Clinical and/or radiological sequelae
[b] During the follow-up period

infections began to be administered in addition to antiretroviral therapy to HIV-infected patients in advanced stages of the disease [1]. The occurrence of adverse effects and the need to consume a large number of tablets prompted some researchers to evaluate the efficacy and safety of intermittent prophylaxis regimens [5, 6, 8–11]. Some of these regimens, such as cotrimoxazole for primary prophylaxis and maintenance therapy of *Pneumocystis carinii* pneumonia or ganciclovir for maintenance therapy of CMV retinitis, became widely used standard regimens in several countries [5, 6].

At present, highly active antiretroviral therapy (HAART) is used in most HIV-infected patients, who have to take 10–15 tablets daily. This is a big obstacle towards achieving compliance, and the consequence is a high failure rate, despite the use of such highly active drugs [12], and impairment of the quality of life of many patients. Thus, in addition to improving the efficacy of antiretroviral regimens, it is important to schedule more convenient prophylactic regimens with a lower tablet consumption.

Although the partial restoration of immunity achieved in many patients taking HAART has recently led to the suggestion that some prophylactic regimens could be stopped, convincing evidence in support of this change in one of the key strategies in the management of HIV-infected patients is still lacking [13–17]. Moreover, although CD4+ cell counts may be significantly increased in many patients on HAART, due to factors such as poor compliance, toxicity, PK interactions, resistance or other mechanisms, treatments may fail and a considerable proportion of patients may remain severely immunosuppressed and thus at risk of developing opportunistic infections [18].

In a previous study, an intermittent regimen consisting of a combination of sulfadiazine, pyrimethamine and folinic acid administered twice weekly was shown to be less effective than a daily regimen in preventing toxoplasmic encephalitis relapses. In the present study, we have shown that a thrice-weekly regimen using 50 mg of pyrimethamine and twice-daily doses of sulfadiazine is comparable in efficacy to a daily regimen using 25 mg of pyrimethamine. Using the former regimen we needed to give only half the number of tablets weekly; moreover, we used a more convenient regimen administered twice a day.

Although it is not always advisable to compare data from different trials, it should be pointed out that the incidence of relapses in patients on the daily regimen in this study was higher than that reported in our previous study (8). Most of the patients who relapsed in this group demonstrated poor compliance. It cannot be ruled out that the twice-daily sulfadiazine regimen also contributed to this high relapse rate, despite the fact that the 12-hour half-life of sulfadiazine justifies the use of a twice-daily regimen [19].

Leport et al. [20] studied the efficacy of a thrice-weekly regimen consisting of pyrimethamine (50 mg) with folinic acid (15 mg) in the primary prophylaxis of toxoplasmic encephalitis in a double-blind randomised study. A total of 554 HIV-1-infected patients seropositive for *Toxoplasma gondii* and with CD4+ cell counts of less than 200 cells/mm^3 were enrolled in the study. After 1 year, no differences were found on intent-to-treat analysis, the incidence of toxoplasmic encephalitis being similar in both groups. However, the analysis showed that the incidence of toxoplasmic encephalitis was lower in the pyrimethamine group (4%) than in the placebo group (12%; $P=0.006$). Therefore, the success of the intermittent regimen administered in the present study probably reflects the synergistic effect of the sulfadiazine-pyrimethamine combination against *Toxoplasma gondii*.

A slight difference was observed in the proportion of relapsed patients showing poor compliance in each group. Only two of seven relapsed patients on the daily regimen took the tablets correctly, compared with six of nine on the intermittent regimen. Although it is difficult to draw definitive conclusions from such a small number of patients, these data suggest that irregular compliance using intermittent prophylaxis regimens may more easily lead to suboptimal therapeutic doses than irregular compliance using daily regimens. This risk must be considered when an intermittent regimen is recommended.

Although *Pneumocystis carinii* pneumonia was suspected clinically in four patients on the intermittent regimen, two patients did not respond to specific therapy and there was no definitive diagnosis of *Pneumocystis carinii* pneumonia in the 124 patients included in the study. These findings are in accordance with previous findings suggesting that intermittent sulfadiazine-pyrimethamine may be effective in the prevention of this AIDS-associated infection [8].

Several patients receiving protease inhibitors in the final months of the study period had a drop in CD4+ cell counts to levels considered a risk for development of toxoplasmic encephalitis. However, no differences which would have had consequences for the comparison of efficacy in the two study groups were observed. In addition, none of the relapses occurred in patients with a CD4+ cell count higher than 100 cells/μl.

Our study has some limitations. The most important is the limited statistical power of the study due to the relatively small number of patients enrolled. However, as stated in the methods section, the sample size is large enough to show that the intermittent regimen is not less effective than the standard daily regimen. Differences above 15% would have been detected, and smaller differences were not considered important enough to justify the additional tablet burden or potential toxicity of a daily regimen. To detect smaller differences (such as 1% or 5%) between the two study groups would require an enormous sample size which would currently be impossible to obtain because of the low incidence of toxoplasmic encephalitis in the HAART era. In future, it will presumably be very difficult to perform a similar study due to the relatively low number of cases of toxoplasmic encephalitis now occurring as a consequence of widespread use of primary prophylaxis regimens and highly active antiretroviral therapy.

Since biases may occur in a non-blinded study, we attempted to limit them by using strict objective criteria for end-point diagnoses, the latter being reviewed by blinded, independent investigators.

In summary, our study suggests that the thrice-weekly sulfadiazine-pyrimethamine-folinic acid regimen tested is not less effective than the standard daily regimen. A more convenient regimen for prevention of toxoplasmic encephalitis may facilitate patient compliance in taking not only this regimen but also antiretroviral and other prophylactic regimens, and may also improve the quality of life in HIV-infected patients in the advanced stages of the disease.

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