

Pyrimethamine-Clarithromycin Combination for Therapy of Acute *Toxoplasma* Encephalitis in Patients with AIDS

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Clarithromycin, a new macrolide, is effective in treating experimental *Toxoplasma gondii* infection. A pyrimethamine-clarithromycin combination was evaluated for the treatment of acute *Toxoplasma* encephalitis in 13 AIDS patients. The scheduled regimen was 2 g of clarithromycin per day and 75 mg of pyrimethamine per day for 6 weeks. The protocol was completed in eight patients and stopped in five patients (because of voluntary withdrawal by two patients, deterioration of neurological condition and thrombocytopenia in two patients, and suspicion of liver toxicity in one patient). The clinical and computed tomography scan responses at week 6 of treatment were 80 and 50%, respectively. Two patients died, one of toxoplasmic encephalitis and the other of cerebral bleeding due to pyrimethamine-induced thrombocytopenia. Adverse events related to therapy were nausea and/or vomiting (38%), skin rash (38%), significant increase of liver tests (24%), hearing loss (15%), and severe hematological abnormalities (31%). In this pilot study, a pyrimethamine-clarithromycin combination was shown to be comparable to the conventional regimen for the treatment of acute *Toxoplasma* encephalitis in AIDS patients.

Toxoplasma encephalitis is a common cause of central nervous system infection in AIDS patients (10). The conventional treatment for toxoplasmosis in these patients is the combination of pyrimethamine and sulfadiazine (9, 11, 14). This treatment is associated with a high rate of adverse events, often requiring discontinuation of one or both drugs. A pyrimethamine-clindamycin combination has been shown to be effective for therapy of acute *Toxoplasma* encephalitis in patients with AIDS, but the frequency of side effects did not appear different from that observed with conventional therapy (7). There was therefore an urgent need to assess new drugs that are active against *Toxoplasma gondii* in clinical studies.

Clarithromycin, a 6-O-methyl derivative of erythromycin, has shown activity against *T. gondii* in vitro and in murine models (2, 3). Also, this drug appeared to have pharmacokinetic advantages compared with older macrolides (6). Thus, a pilot study was designed to assess the efficacy and safety of a pyrimethamine-clarithromycin combination in 13 AIDS patients with a primary episode of *Toxoplasma* encephalitis.

(A preliminary report of this research has been presented [8]).

MATERIALS AND METHODS

Study population. The study population consisted of human immunodeficiency virus type 1 seropositive patients with a primary episode of *Toxoplasma* encephalitis. The diagnosis was based on clinical findings such as fever and/or neurological signs suggestive of central nervous system infection and on computed tomography (CT) scan lesions consistent with the presence of *Toxoplasma* encephalitis (13). All patients had antibodies to *T. gondii* in their sera.

Criteria for eligibility included age between 18 and 60 years, absence of known sensitivity to macrolide antibiotics, absence of concomitant active opportunistic infection, and a minimum life expectancy greater than 6 weeks. Patients should not have received anti-*Toxoplasma* therapy for more than 48 h prior to their inclusion in the study. The use of other drugs that are potentially active against *T. gondii*, such as dapsone, other macrolides, sulfonamides, doxycycline, or clindamycin, was not authorized. Patients were eligible if their aminotransferase and alkaline phosphatase levels in serum were at least threefold lower than the normal values. Patients had to have a serum creatinine level lower than 120 $\mu\text{mol/liter}$, a hemoglobin level greater than 8 g/dl, a neutrophil count greater than 1,000 cells per mm^3 , and platelet counts greater than 50,000 cells per mm^3 .

The study protocol was approved by the institution review board of Bichat-Claude Bernard hospital, and written consent was obtained from all patients.

Treatment regimen. Clarithromycin was provided by Abbott Laboratories (Rungis, France). The dosage of clarithromycin used was the maximal dosage which had been used previously for 6 weeks in human immunodeficiency virus-infected patients for treatment of mycobacterial infections (5). Thus, patients were given 2 g of clarithromycin per day in two divided doses. Pyrimethamine was administered after a loading dose of 200 mg, at a dosage of 75 mg once daily. Folic acid (20 mg per day) was systematically added. All drugs were given orally. Duration of therapy was planned for 6 weeks. Corticosteroids were authorized only when necessary, using 1 mg of tetracosactide per day parenterally for 5 to 10 days.

Assessment of efficacy. Efficacy was assessed at the end of week 3 and week 6 of therapy, both clinically and by CT scan. Clinical evaluation was made every day during the first week and twice a week for 6 weeks if clinical improvement was present. The clinical and CT responses were graded

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TABLE 1. Clinical and CT scan evaluation of patients with *Toxoplasma* encephalitis treated with the pyrimethamine-clarithromycin combination

Patient no.	Clinical sign(s)	CT scan lesions	Duration of therapy (days)	Clinical response at week:		CT scan response at week:	
				3	6	3	6
1	Fever, headache, hemiparesis	Multiple	42	Complete	Complete	Incomplete	Incomplete
2	Fever, headache, confusion, hemiparesis	Multiple	14 ^a	Complete	NE ^b	Partial	NE
3	Hemiparesis, seizures	Unique	11 ^c	Progression, death	NE	Absent	NE
4	Confusion, ataxia, seizures	Unique	47	Complete	Complete	Incomplete	Incomplete
5	Fever, ataxia	Multiple	40	Partial	Partial	Partial	Partial
6	Fever, headache	Unique	41	Complete	Complete	Partial	Complete
7	Fever, aphasia, hemiparesis	Multiple	43	Partial	Partial	Incomplete	Incomplete
8	Fever, headache, confusion	Multiple	57	Complete	Complete	Incomplete	Incomplete
9	Fever	Unique	43	Complete	Complete	NE	Partial
10	Fever, headache, hemiparesis	Multiple	34 ^a	Complete	NE	Incomplete	NE
11	Fever, headache, confusion, seizures	Multiple	16 ^d	Absent, death	NE	Partial	NE
12	Headache, hemiparesis	Unique	44	Partial	Complete	Incomplete	Partial
13	Fever, headache, hemianopsia	Unique	16 ^e	Complete	NE	Incomplete	NE

^a Voluntary withdrawal from protocol.

^b NE, not evaluable.

^c Pyrimethamine therapy was stopped on day 11.

^d Patient was switched to 25 mg of pyrimethamine per day on day 16 of the protocol.

^e Therapy was stopped because of suspicion of liver toxicity.

independently according to the same semiquantitative scale, which had been defined by the California Collaborative Treatment Group (4). One of the five following conditions was assigned for each patient, on the basis of clinical or CT scan evaluation. Complete response was defined as complete resolution of all clinical or radiological manifestations attributable to *Toxoplasma* encephalitis. Partial response was defined as an improvement of clinical or radiological signs of greater than 50%. Incomplete response was an improvement of clinical or radiological signs of less than 50%. Absence of response was defined as no change in clinical status or CT scan. Progression was defined as a deterioration of neurological status or CT scan.

Brain CT scan was done at the time of diagnosis and at week 3 and week 6 of therapy. All scans were evaluated by the same radiologist, who was unaware of the identification and dates of the scans and of the patient's clinical course. The radiologist put the scans of each patient in chronological order. Then he evaluated the second and the third scans compared with the first scan by using the previously defined semiquantitative scale.

Assessment of adverse reactions. Adverse reactions were assessed by monitoring both clinical manifestations and laboratory parameters. Complete blood counts and renal and liver tests were performed every 3 days. Audiometric testing was performed before and after treatment whenever possible. Intensities of adverse events were graded as minimal, mild, moderate, or severe. The relationship of adverse events to the study drug was assessed as probable, possible, or unrelated.

Discontinuation of therapy. Patients were withdrawn from the protocol if they failed to comply with the therapeutic plan or if the investigator considered withdrawal to be in the interest of the patient because of clinical failure or severe adverse reaction. Premature discontinuation of the protocol was planned if clinical failure was reported after 3 weeks of therapy or even before 3 weeks if there was deterioration of the level of consciousness or a worsening of neurological defects greater than 50% of baseline findings or if there was an appearance of cranial hypertension.

RESULTS

The study population consisted of 13 patients, of whom 12 were male. The mean age was 36 years (range, 26 to 59). Previous diagnosis of AIDS had been made for nine patients. *Pneumocystis carinii* pneumonia had been diagnosed in five patients, extra pulmonary tuberculosis had been diagnosed in three, and esophageal candidiasis had been diagnosed in one. Two patients had Kaposi's sarcoma. Baseline characteristics in the patients are presented in Table 1.

Eight patients completed the 6-week regimen. The scheduled regimen was stopped prematurely between week 3 and week 6 in five patients, because of voluntary withdrawal in two patients, severe thrombocytopenia in two patients, and liver toxicity, possibly related to clarithromycin, in one patient. No other drugs active against *T. gondii* were used concomitantly. Five patients were given corticosteroids for a mean duration of 6 days (range, 2 to 15 days).

Clinical evaluation at week 3 was made in all patients (Table 1) and revealed complete remission of clinical signs in eight patients and partial response in three others. Two patients had an unfavorable response.

Clinical evaluation at week 6 was possible for the eight patients who completed the protocol. Complete response was noted in six patients and partial response was noted in two patients.

The cases of the two patients with unfavorable responses are reported here. Both had an initial clinical improvement. One patient was switched to clarithromycin monotherapy on day 11 of the protocol because of pyrimethamine-induced thrombocytopenia (11,000 platelets per mm³) and because of previous allergy to sulfonamides. His condition then worsened, and a premortem CT scan showed massive bilateral cerebral low densities. Death occurred during week 4. In the other patient, the course of the disease was complicated by severe thrombocytopenia which required reduction of the dose of pyrimethamine to 25 mg/day on day 16. Despite persistent clinical improvement, he died on day 26 of meningeal and ventricular bleeding. A CT scan done before death showed a partial response of his toxoplasmic lesions. Autopsy was not done in these two patients.

TABLE 2. Clinical and biological adverse reactions in 13 AIDS patients with *Toxoplasma* encephalitis treated with the pyrimethamine-clarithromycin combination

Adverse reaction	No. (%) of patients
Nausea and/or vomiting	5 (38)
Skin rash	5 (38)
Hearing loss	2 (15)
Abnormalities in liver tests	10 (77)
Minimal ^a	7 (54)
Significant ^b	3 (24)
Hematological abnormalities	7 (54)
Minimal ^c	3 (24)
Significant ^d	4 (31)

^a Less than a twofold increase from baseline values.

^b More than a twofold increase from baseline values.

^c Hemoglobin less than 12 g/dl or 10% of baseline value, neutrophils less than 1,250/mm³, and platelets less than 100,000/mm³.

^d Hemoglobin less than 8 g/dl, neutrophils less than 1,000/mm³, and platelets less than 50,000/mm³.

Results of CT scan evaluation are shown in Table 1. The radiologist, unaware of the true chronological sequence, put all scans for all patients in the correct chronological order. At week 3, CT scan evaluation was done for 12 patients. For one patient with complete clinical response, a CT scan could not be performed at week 3. Partial response was seen in four patients, incomplete response was seen in seven, and there was an absence of response in one. CT scan evaluation at week 6 was possible for all eight patients who completed the protocol. Complete response was seen in one patient, partial response was seen in three, and incomplete response was seen in four.

Adverse reactions are listed in Table 2. Nausea or vomiting were transitory, mild, and probably related to therapy. Skin rash was transitory and in four of the five patients was probably related to therapy. In the fifth patient, concomitant conjunctivitis was present and a viral etiology was suggested. Therapy was continued without modification of the scheduled regimen in all patients with skin rash. Hearing loss was detected in two of the three patients who were tested by audiometry. Clinical hearing loss appeared during the second week of treatment in these two patients and was confirmed by audiometric testing. It was categorized as being sensorial, mild in intensity, and probably related to clarithromycin therapy. One patient with hearing loss was a 55-year-old man who voluntarily withdrew from clarithromycin therapy. He had had a normal pretherapy audiogram. The other patient had concomitant severe liver enzyme abnormalities, and clarithromycin treatment was stopped. Two weeks later, unvariable perception hearing loss was present.

Biological monitoring revealed a modification of baseline values of liver function tests in 10 patients (Table 2). In seven patients these modifications were minimal (less than twofold the baseline values), in one patient they were mild (more than twofold and less than fivefold the baseline values), in one patient they were moderate (more than fivefold and less than 10-fold the baseline value), and in one patient they were severe (more than 10-fold the baseline value). The two patients with moderate and severe increases of baseline values had minimal pretherapy elevations. In the patient with severe liver enzyme abnormalities, in whom therapy was stopped, hepatic biopsy showed cytomegalovirus hepatitis. Disseminated *Mycobacterium avium-Mycobacterium intracellulare* infection and intestinal crypto-

sporidiosis with cholestasis were diagnosed later in the patient with the moderate increase in liver function tests. Hematological abnormalities were reported in seven patients. Significant anemia (lower than 8 g/dl) was seen in one patient, neutropenia (lower than 1,000/mm³) was seen in four patients, and thrombocytopenia (lower than 50,000/mm³) was seen in three patients. Thus, overall, discontinuation of the protocol for toxicity was required in three (23%) of the patients: one patient with severe liver enzyme abnormalities and two patients with severe thrombocytopenia.

DISCUSSION

This study shows that oral therapy with pyrimethamine-clarithromycin is effective for the treatment of acute *Toxoplasma* encephalitis in patients with AIDS. The overall therapeutic clinical response rates of 84% at week 3 of therapy and of 80% at week 6 and the overall mortality rate of 15% are similar to those observed in AIDS patients treated with pyrimethamine and sulfadiazine or pyrimethamine and clindamycin (7, 9, 14).

Improvement, as determined by CT scan, was delayed in comparison with clinical response. Only 30 and 50% of patients had CT scan improvement greater than 50% at week 3 and week 6, respectively. Response of AIDS patients with *Toxoplasma* encephalitis to therapy, as determined by CT scan, is not as well documented as clinical response in the literature (13). In a recent study which compared pyrimethamine-sulfadiazine with pyrimethamine-clindamycin with the same scale of evaluation, Danneman et al. found complete and partial clinical responses in 79 and 77% of patients, respectively, and a complete and partial radiological responses in 76 and 73% of patients, respectively, after 6 weeks of therapy (4). Several factors can explain these discordances. First, it is important to note that our series of patients is limited; two patients died before treatment was completed and autopsy study was not performed. Thus, other diagnoses could not be excluded at least in one patient. Second, the blind evaluation of CT scans in our study without information of clinical evolution may have suppressed the subjective favorable interpretation of CT scan in previous studies (9). In the present study there was a trend toward a less favorable evaluation of CT scans by the external radiologist, compared with the evaluation by the clinicians caring for the patients. Further studies of therapy of acute *Toxoplasma* encephalitis should consider careful semiquantitative and objective assessment of both clinical and CT scan responses. Whether clarithromycin added some beneficial effect to the effect of pyrimethamine is questionable, as it is for all other drugs which have been used in combination with pyrimethamine (7). The use of a combination of pyrimethamine and another drug is a general recommendation, since the efficacy of pyrimethamine alone for therapy of acute brain toxoplasmosis in humans has not been established. Our study was not designed to address the intrinsic effect of clarithromycin; it simply suggests that this effect was not markedly different from that of sulfadiazine when added to pyrimethamine.

Adverse reactions related to therapy were present in 90% of the patients treated with pyrimethamine-clarithromycin. However, they were often minor and did not require changes in the therapeutic regimen. Gastrointestinal tolerance was acceptable, and minor skin rash was present in 31% of patients. Hearing loss was probably related to the clarithromycin therapy, determined on the basis of a normal pretherapy audiogram in one patient. Interpretation of hearing loss

is difficult for patients with central nervous system infections. The mechanisms of ototoxicity of macrolides are not well identified. Effects in the central auditory pathways have been suggested for erythromycin-induced ototoxicity. Hearing loss is one of the less-known adverse effects of erythromycin. The parameters commonly present in patients with erythromycin-induced hearing loss are high doses of the drug, intravenous administration, and presence of renal insufficiency (1). In our patients, renal function was preserved and clarithromycin was administered orally. The dosage of 2 g per day is probably the critical factor for such toxicity. Possible significant liver toxicity of clarithromycin was observed in three patients, as has been previously reported with other macrolide antibiotics (12). Two of our patients had other factors that could predispose them to hepatic injury. Thus, pretherapy intact liver function tests, i.e., liver function tests no greater than two times the baseline values, should be a limiting criterion for the use of clarithromycin in the treatment of *Toxoplasma* encephalitis in patients with AIDS. Significant hematologic toxicity was present in four patients (31%) requiring premature discontinuation of the protocol and in the two patients with unfavorable evolution. Combination of pyrimethamine with nonhematotoxic drugs such as clarithromycin or clindamycin illustrates the important bone marrow toxicity of pyrimethamine at the doses used for patients with *Toxoplasma* encephalitis. The optimal dose of pyrimethamine and of folinic acid to prevent pyrimethamine hematologic toxicity has yet to be determined.

Though we did not conduct a concurrent study using a combination of pyrimethamine and clindamycin or pyrimethamine and sulfadiazine, the results of this pilot study of the pyrimethamine-clarithromycin combination were comparable to the results of previous separate studies of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin combinations for the therapy of acute *Toxoplasma* encephalitis in patients with AIDS. The optimal dose of clarithromycin has yet to be defined. Prospective controlled comparative studies with conventional therapy are necessary.

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