

CLARITHROMYCIN PROPHYLAXIS AGAINST CRYPTOSPORIDIUM ENTERITIS IN PATIENTS WITH AIDS

Wilbert C. Jordan, MD, MPH
Los Angeles, California

Cryptosporidium enteritis (CE) in patients with acquired immunodeficiency syndrome (AIDS) can be a life-threatening opportunistic infection. A retrospective review of 471 charts of patients with AIDS in our clinic, prior to the availability of clarithromycin for the treatment of *Mycobacterium avium* complex (MAC), revealed that seven patients with CD4 counts <25/mm³ developed CE. The median survival period from diagnosis to death in these patients was 10.6 days. The incidence of CE in patients with CD4 counts <50/mm³ treated with clarithromycin prophylaxis for MAC was compared with patients not receiving clarithromycin prophylaxis. Of 136 patients with AIDS, 63 received clarithromycin 500 mg twice daily, and 73 patients not treated with clarithromycin represented the control group. None of the patients who received clarithromycin developed CE compared with four patients who developed CE in the control group. All four patients in the control group who developed CE had CD4 counts <25/mm³. All patients who received clarithromycin remained stool negative for *Cryptosporidium*. In a subsequent 2-year follow-up of an additional 217 AIDS patients with CD4 counts <50/mm³ receiving clarithromycin 500 mg twice

daily as MAC prophylaxis, no patient developed CE. These results provide strong evidence supporting the use of clarithromycin as prophylaxis against cryptosporidium enteritis in patients with AIDS. (*J Natl Med Assoc.* 1996;88:425-427.)

Key words • clarithromycin

• cryptosporidium enteritis

• *Mycobacterium avium* complex prophylaxis

As of June 1994, a total of 401,749 cases of acquired immunodeficiency syndrome (AIDS) were reported in the United States.¹ Although there is still no cure for AIDS, the use of antiretroviral therapy and effective prevention of infectious complications may improve survival.^{2,3} As the survival of patients with AIDS increases, so does the incidence of opportunistic infections such as *Mycobacterium avium* complex (MAC) and parasitic diseases such as cryptosporidiosis.

Mycobacterium avium complex has become the most common serious infection in patients with AIDS.²⁻⁸ The Multicenter AIDS Cohort Study recently reported that MAC was the most common infection in AIDS patients with <100 CD4 + T-cells/mm³ who were receiving both antiretroviral therapy and *Pneumocystis carinii* pneumonia prophylaxis.² Clarithromycin, a macrolid antibiotic, has significant clinical efficacy against MAC and is approved for the treatment of MAC infection in combination with at least one other antimycobacterial agent.⁹ Clarithromycin also has been shown to be effective as MAC prophylaxis in patients with AIDS.¹⁰ Recently, application has been submitted to the FDA for the approval of clarithromycin for MAC prophylaxis.

From the Department of Internal Medicine and Family Practice, Charles R. Drew University of Medicine and Science, King/Drew Medical Center, Los Angeles, California. Requests for reprints should be addressed to Dr Wilbert C. Jordan, Dept of Internal Medicine and Family Practice, Charles R. Drew University of Medicine and Science, King/Drew Medical Ctr, 12021 S. Wilmington Ave, Los Angeles, CA 90059.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH CRYPTOSPORIDIUM ENTERITIS PRIOR TO AVAILABILITY OF CLARITHROMYCIN

Patient	CD4 Count (mm ³)	WBC Count	Days From Diagnosis to Death
1	10	2.1	8
2	15	1.7	4
3	21	1.8	17
4	7	2.0	21
5	5	2.3	11
6	5	1.9	13
7	0	1.1	10

Cryptosporidiosis or cryptosporidium enteritis (CE) is a diarrheal disease produced by the parasite of the *Cryptosporidium* genus. In normal individuals, CE may be self-limiting; however, in immunocompromised patients, cryptosporidiosis often results in a chronic, life-threatening gastroenteritis with high mortality.^{11,12} The absolute CD4 cell count appears to correlate with disease response and outcome^{11,12}: patients with CD4 cell counts <50/mm³ were identified during their regular clinic visit. Patients seen on even numbered dates during the study were given clarithromycin 500 mg twice daily for MAC prophylaxis. Control patients, those seen on odd numbered dates, were not given clarithromycin. Patients were excluded from study participation if they were receiving clarithromycin as part of another study or as treatment, had a history of allergy or sensitivity to clarithromycin, were diagnosed with *Cryptosporidium* prior to study initiation, or had a history of severe diarrhea occurring within the previous 2 weeks. All patients provided written informed consent prior to study initiation.

RESULTS

Seven patients (1.5%) out of 471 charts reviewed had been diagnosed with CE. All patients had CD4 counts <25/mm³ and a mean white blood cell count of 1.84 at the time of diagnosis. All patients experienced severe and unrelenting diarrhea, rapid weight loss, and death with a mean survival of 10.6 days from diagnosis (Table 1). One hundred thirty-seven patients were eligible for the prospective study and underwent follow-up for at least 12 months. Sixty-three patients received clarithromycin and 73 did not. The patients were stratified by their CD4 cell count and incidence of CE (Table 2). No patient receiving clarithromycin for MAC prophylaxis developed CE, and all patients in this group remained stool negative for CE. Four of 48

TABLE 2. CHARACTERISTICS OF PATIENTS AND INCIDENCE OF CRYPTOSPORIDIUM ENTERITIS (CE) BY TREATMENT GROUP

Parameter	No. Patients	
	Receiving Clarithromycin*	Not Receiving Clarithromycin†
Patients with CD4 >26	25	25
No. developing CE	0	0
Patients with CD4 ≤25	38	48
No. developing CE	0	4

*n=63.

†n=73.

patients (8%) in the control group with CD4 counts of <25/mm³ developed CE.

DISCUSSION

The estimated prevalence of cryptosporidiosis among patients with AIDS in the United States is 10% to 15%.¹⁵ In this retrospective analysis of 471 charts of patients with AIDS, the overall incidence of CE was less than 2% (7/471). However, when these patients were stratified by the CD4 counts, all seven cases of CE occurred in the subgroup of 86 patients with CD4 counts <25/mm³. This 8% (7/86) prevalence of CE among patients with CD4 counts <25/mm³ prior to the availability of clarithromycin was identical to that observed in the prospective study control group (8%, 4/48) and is slightly lower than the published prevalence rates. Of significant interest is that no patient in the clarithromycin prophylaxis group, regardless of their CD4 cell count, developed CE during the course of the study.

Although immunocompetent patients often can shed the parasite and recover spontaneously, CE in patients with AIDS is a life-threatening opportunistic infection. Immunocompromised patients with CE develop a profuse watery diarrhea that results in extensive fluid and nutrient loss. Patients may complain of abdominal cramping, nausea, vomiting, and low-grade fever. Physician examination of these patients generally reveals signs of dehydration. Eosinophilia or peripheral blood leukocytosis may be found with laboratory assessment. Extraintestinal cryptosporidial infections with associated pathologic changes of the liver, esophagus, pancreas, and respiratory tract also may occur.¹⁶ The diagnosis of cryptosporidiosis is made by identification of oocysts in fecal smears or by tissue biopsy.

The treatment of patients with CE is primarily supportive; hydration and nutritional supplementation are the standards of therapy. The course of CE in immuno-

competent patients (ie, those with intact cell-mediated and humoral immunity) is characterized by a rapid onset and short duration.^{15,17} In patients with AIDS, spontaneous recovery from CE is infrequent, and the disease course may result in death.^{11,12} In one study, patients with AIDS and CD4 counts $<50/\text{mm}^3$ who developed CE experienced a fulminant disease course with a median survival time of 5 weeks from disease onset,¹¹ although only a weak correlation was documented between patient survival and CD4 counts at the time of disease onset. Results of our retrospective chart evaluation were consistent with those found in the study by Blanshard et al¹²: all patients with AIDS who developed CE had CD4 counts $<25/\text{mm}^3$ and died within 3 weeks of disease diagnoses.

The results of our trial have altered our treatment strategy in patients with AIDS and depressed CD4 counts. Currently, we initiate clarithromycin (ie, 500 mg twice daily) for MAC and CE prophylaxis in patients with CD4 counts $<50/\text{mm}^3$. In a subsequent 2-year follow-up of 217 AIDS patients with CD4 counts $<50/\text{mm}^3$ receiving clarithromycin prophylaxis, no patient has developed CE.

CONCLUSION

Results of this study provide strong evidence supporting the use of clarithromycin as prophylaxis against cryptosporidium enteritis in patients with AIDS.

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