

ATOVAQUONE AND AZITHROMYCIN FOR THE TREATMENT OF BABESIOSIS

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ABSTRACT

Background Babesiosis is a tick-borne, malaria-like illness known to be enzootic in southern New England. A course of clindamycin and quinine is the standard treatment, but this regimen frequently causes adverse reactions and occasionally fails. A promising alternative treatment is atovaquone plus azithromycin.

Methods We conducted a prospective, nonblinded, randomized trial of the two regimens in 58 subjects with non-life-threatening babesiosis on Nantucket, Massachusetts; on Block Island, Rhode Island; and in southern Connecticut. The subjects were assigned to receive either atovaquone (750 mg every 12 hours) and azithromycin (500 mg on day 1 and 250 mg per day thereafter) for seven days (40 subjects) or clindamycin (600 mg every 8 hours) and quinine (650 mg every 8 hours) for seven days (18 subjects).

Results Adverse effects were reported by 15 percent of the subjects who received atovaquone and azithromycin, as compared with 72 percent of those who received clindamycin and quinine ($P < 0.001$). The most common adverse effects with atovaquone and azithromycin were diarrhea and rash (each in 8 percent of the subjects); with clindamycin and quinine the most common adverse effects were tinnitus (39 percent), diarrhea (33 percent), and decreased hearing (28 percent). Symptoms had resolved three months after the start of therapy in 65 percent of those who received atovaquone and azithromycin and 73 percent of those who received clindamycin and quinine ($P = 0.66$), and after six months no patient in either group had symptoms. Three months after the completion of the assigned regimen, no parasites could be seen on microscopy, and no *Babesia microti* DNA was detected in the blood of any subject.

Conclusions For the treatment of babesiosis, a regimen of atovaquone and azithromycin is as effective as a regimen of clindamycin and quinine and is associated with fewer adverse reactions. (N Engl J Med 2000;343:1454-8.)

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have been described elsewhere in North America, in Europe, and in Asia.⁷⁻¹⁰ Although a course of clindamycin and quinine is generally prescribed for patients with babesiosis, this regimen frequently causes adverse reactions (including tinnitus and gastroenteritis) and occasionally fails.¹¹⁻¹³ A course of atovaquone and azithromycin is a promising alternative for the treatment of this zoonosis; this combination effectively eliminates babesial infection in hamsters, and adverse reactions are rare when these drugs are used to treat malaria in humans.¹⁴⁻¹⁶

We conducted a prospective, nonblinded, randomized trial in southern New England to compare the safety and efficacy of a regimen of atovaquone and azithromycin with those of a conventional regimen of clindamycin and quinine in people with babesiosis.

METHODS

Study Population

Subjects with symptomatic babesiosis were enrolled in this prospective, nonblinded, randomized study conducted at clinics on Nantucket, Massachusetts; on Block Island, Rhode Island; and in southern Connecticut. Enrollment took place during the period of peak transmission (May to September) each year from 1995 through 1998. After written informed consent was obtained from the patients, a medical history was obtained and a physical examination performed. A standardized questionnaire was used to obtain information on symptoms.¹⁷ Laboratory studies were performed at the University of Connecticut Health Center and included microscopic examination of Giemsa-stained thin blood smears, attempted amplification of *Bab. microti* DNA, and evaluation of serologic reactivity against *Bab. microti*, *Borrelia burgdorferi*, and *Ehrlichia equi* antigens. Tests for the latter two microorganisms, which are the agents of Lyme disease and human granulocytic ehrlichiosis, respectively, were included because these infections are transmitted by the same tick that transmits *Bab. microti* infection (*Ixodes dammini*, also known as *I. scapularis*) and because coinfection with these microorganisms may occur in both ticks and humans.

Random assignment of consecutive eligible subjects to one of the treatment regimens was performed at each study site without blocking and with the use of a table of random numbers ensuring that about two thirds of the subjects at each study site received

HUMAN babesiosis due to *Babesia microti* is a tick-borne, malaria-like infection that may cause severe illness and death. It is enzootic mainly in southern New England, southern New York, Wisconsin, and Minnesota.¹⁻⁶ Occasional infections in humans due to such piroplasms as *Bab. divergens*, an isolate from Washington state (WA1), and an isolate from Missouri (MO1)

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atovaquone (Mepron, Glaxo Wellcome, Research Triangle Park, N.C.) at a dose of 750 mg every 12 hours and azithromycin (Zithromax, Pfizer, New York) at a dose of 500 mg on day 1 and 250 mg per day thereafter and about one third received clindamycin (Cleocin, Pharmacia & Upjohn, Bridgewater, N.J.) at a dose of 600 mg every 8 hours and quinine at a dose of 650 mg every 8 hours. All the antibiotics were given by mouth for seven days. The subjects were asked to complete a standardized daily diary of symptoms, including any possible adverse reactions to the study drugs. Follow-up visits were scheduled to take place one week, two weeks, and one, three, and six months after the completion of therapy and monthly thereafter until symptoms were gone and parasitemia resolved (as documented by staining of blood smears and amplification of DNA).

Subjects were enrolled in the study if they had the following: symptoms consistent with the presence of babesiosis; positive serologic reactivity against *Bab. microti* antigen (an elevation by a factor of four in the *Bab. microti* antibody titer, according to an indirect fluorescence antibody assay, in serum samples obtained during the acute and convalescent phases, or an antibody titer greater than 1:1024); and evidence of *Bab. microti* parasites on a Giemsa-stained thin blood smear or detection of *Bab. microti* DNA in a blood sample (by polymerase-chain-reaction [PCR] amplification). Subjects were excluded from the study if they had a babesial illness that was life-threatening (characterized by encephalopathy, shock, congestive heart failure, pulmonary edema, diffuse intravascular coagulation, or renal failure), required an exchange transfusion or assisted ventilation, had an allergy to one of the study drugs, or were 18 years of age or younger. A diagnosis of acute Lyme disease required either a physician's diagnosis of erythema migrans (defined as an expanding, ringlike erythematous rash \geq 5 cm in diameter) or symptoms consistent with the presence of Lyme disease, accompanied by an elevation by a factor of four in the *Borr. burgdorferi* antibody titer.¹⁸ Concurrent infection with Lyme disease or human granulocytic ehrlichiosis was diagnosed in subjects who had characteristic symptoms and in whom laboratory findings suggested infection by the agent of one of these diseases.

Diagnostic Studies

Microscopical Evaluation

Thin blood smears were prepared from blood samples that were treated with EDTA as an anticoagulant, fixed in absolute methanol, and placed for one hour in 5 percent Giemsa at a pH of 7.0.¹⁷ The slides were then washed and dried and a coverslip added. Each slide was viewed at a magnification of 400. At least 100 microscopical fields had to be examined before a sample could be considered free of piroplasms. When evidence of piroplasms was seen, their presence was confirmed and the diagnosis of babesiosis established by viewing the slide with an oil-immersion objective that provided a magnification of 1000. Thin blood smears were prepared at each site and analyzed at the University of Connecticut Health Center.

Serologic Evaluation

Babesial infection was diagnosed serologically by an indirect immunofluorescence assay.¹⁹ Serum samples were diluted 1:32 in phosphate-buffered saline, and the titers of all reactive serum samples were determined to their end point. The secondary antibody was fluorescein isothiocyanate-labeled goat antihuman IgG or IgM (Kirkegaard & Perry, Gaithersburg, Md.) diluted in phosphate-buffered saline and Evans blue to a final concentration of 0.0005 percent. Slides were examined at a magnification of 630 under epifluorescence. For comparison, each series of tests included serum from a subject who had babesial infection (a positive control), serum from an adult who appeared never to have been infected with babesia (a negative control), and phosphate-buffered saline. A positive specimen was defined as one that reacted at a dilution of 1:32 or greater.

Molecular Evaluation

Samples of whole blood were analyzed and processed by personnel who were unaware of the clinical status of the subjects. A 238-bp portion of the *Bab. microti* nuclear small-subunit ribosomal gene was targeted for amplification with a PCR protocol as described previously,^{20,21} except that the volume of blood analyzed was 0.5 ml rather than 0.2 ml.

Assays for Coinfecting Agents

Serologic evidence of exposure to the spirochete that causes Lyme disease was assessed by an enzyme-linked immunosorbent assay, as previously described.¹⁷ A positive serum sample was defined as one that reacted at a dilution equal to or greater than 1:320 for IgG and equal to or greater than 1:160 for IgM. Evidence of exposure to the agent of human granulocytic ehrlichiosis was defined as the presence of morulae in thin blood smears, amplification of a DNA sequence characteristic of this pathogen in subjects' blood, or detection of seroreactivity by indirect immunofluorescence with use of fluorescein-labeled polyvalent antihuman IgG as previously described.^{22,23}

Statistical Analysis

An appropriate sample size was estimated before the start of our study on the basis of a previous study in which parasitemia resolved 12 weeks after the start of treatment in 73 percent of patients treated with clindamycin and quinine.⁶ Half or double that rate of clearance after therapy with atovaquone and azithromycin was assumed to represent a clinically significant difference between the two treatment groups. We estimated that 60 subjects would be needed to provide the study with 80 percent power to detect a statistically significant difference, with an error rate of 5 percent. Descriptive statistics were calculated for all variables; continuous variables were summarized as means and standard deviations, and categorical variables were summarized as frequencies. Subjects treated with atovaquone and azithromycin and those treated with clindamycin and quinine were compared in terms of age, sex, symptoms, and adverse reactions with use of Student's t-test or Fisher's exact test. The rate of persistence of babesial infection in the two treatment groups, as indicated by findings on Giemsa-stained thin blood smears and by amplification of DNA, was evaluated with use of product-limit (Kaplan-Meier) survival estimates, without censoring, on the basis of the last time at which *Bab. microti* DNA could be amplified from each subject. All reported P values are two-sided.

RESULTS

Study Population

Of the 59 subjects who were enrolled in the study, 41 were randomly assigned to receive atovaquone and azithromycin, and 18 were randomly assigned to receive clindamycin and quinine. Forty-three of the enrolled subjects were from Nantucket, 12 were from Connecticut, and 4 were from Block Island. One of the subjects assigned to receive atovaquone and azithromycin was excluded from all analyses because he became severely ill and required assisted ventilation two days after enrollment. The subjects in the two treatment groups had similar age and sex distributions, had a similar array of symptoms, and had a similar degree of parasitemia when therapy commenced (Tables 1 and 2).

Parasites were visualized on the thin blood smear in 82 percent of the subjects assigned to receive atovaquone and azithromycin and 89 percent of those as-

TABLE 1. CHARACTERISTICS OF THE SUBJECTS AT THE START OF TREATMENT FOR *BABESIA MICROTI* INFECTION AND FREQUENCY OF ADVERSE REACTIONS TO THE STUDY DRUGS.*

VARIABLE	ATOVAQUONE AND AZITHROMYCIN (N=40)	CLINDAMYCIN AND QUININE (N=18)
Male sex (% of subjects)	55	50
Age (yr)		
Median	56	54
Range	25–85	32–80
No. of symptoms	8.9±3.2	9.3±2.8
Parasitemia (% of infected erythrocytes)		
Median	0.5	0.5
Range	0.05–12.0	0.05–9.0
Adverse reactions (% of subjects)		
Reported	15 (4–26)	72 (51–93)†
Severe	2 (0–10)	33 (11–55)†

*Plus–minus values are means ±SD. Numbers in parentheses are 95 percent confidence intervals. Severe adverse reactions were defined as those severe enough that the doses of drugs were decreased or the drugs discontinued. These reactions included tinnitus or decreased hearing (in all the subjects) and diarrhea, cardiac arrhythmia, vertigo, and a hive-like rash (in one subject each).

†P<0.001.

signed to receive clindamycin and quinine; *Bab. microti* DNA was amplified from whole-blood samples from the other subjects. One subject who was assigned to atovaquone and azithromycin and two who were assigned to clindamycin and quinine were asplenic, and one subject in each treatment group was receiving maintenance therapy with corticosteroids. None of the subjects were infected with the human immunodeficiency virus (HIV) or were pregnant. The two groups were similar with respect to the frequency of coinfection with the agent of Lyme disease (22 percent in the atovaquone-and-azithromycin group and 17 percent in the clindamycin-and-quinine group) or with the agent of human granulocytic ehrlichiosis (none of the subjects in either group). Fever occurred in 92 percent of those assigned to atovaquone and azithromycin and in 94 percent of those assigned to clindamycin and quinine. The distribution of oral temperatures recorded by study physicians just before the start of antibiotic therapy in the atovaquone-and-azithromycin group was similar to that in the clindamycin-and-quinine group (<37.2°C in 33 percent and 27 percent, respectively; 37.2°C to 38.2°C in 33 percent and 28 percent; 38.3°C to 39.4°C in 31 percent and 39 percent; and 39.5°C to 40.6°C in 3 percent and 6 percent). The median hematocrit in the atovaquone-and-azithromycin group (37.7 percent [range, 29.9 to 43.7]) was similar to that in the clin-

TABLE 2. SYMPTOMS OF ACUTE ILLNESS IN SUBJECTS WITH *BABESIA MICROTI* INFECTION.*

SYMPTOM	ATOVAQUONE AND AZITHROMYCIN (N=40)	CLINDAMYCIN AND QUININE (N=18)
	percent of subjects	
Start of therapy		
Fever	92	94
Fatigue	92	89
Sweats	80	89
Muscle aches	80	83
Headache	78	83
Chills	75	89
Anorexia	75	83
Neck stiffness	52	44
Emotional lability	52	44
Cough	50	50
Nausea	45	61
Joint pain	45	61
Sore throat	38	17
Vomiting	20	22
Conjunctivitis	12	6
Joint swelling	10	11
Splenomegaly	2	6
During therapy†		
Diarrhea	8	33‡
Tinnitus	0	39§
Decreased hearing	0	28§
Rash	8	11
Vertigo	2	17

*The mean (±SD) number of symptoms at the start of therapy was 8.9±3.2 in the atovaquone-and-azithromycin group and 9.3±2.8 in the clindamycin-and-quinine group (P=0.6). The mean number of symptoms during therapy was 1.0±0 in the atovaquone-and-azithromycin group and 1.5±0.8 in the clindamycin-and-quinine group (P=0.09).

†P<0.001 for the comparison between the two treatment groups.

‡P<0.02.

§P<0.002.

damycin-and-quinine group (33.2 percent [range, 20.0 to 45.2]). All of the subjects who were coinfecting with the agents of babesiosis and Lyme disease received appropriate therapy for Lyme disease. The subjects assigned to atovaquone and azithromycin had an array of symptoms and tick-associated infections similar to that in subjects assigned to clindamycin and quinine.

Frequency and Severity of Adverse Drug Reactions

We next distinguished the symptoms that could be attributed to babesiosis from those that appeared to be caused by the study drugs. Of the 18 subjects who received clindamycin and quinine, 13 (72 percent) reported symptoms that are known to be adverse effects of quinine, including decreased hearing, tinnitus, vertigo, and diarrhea (Table 2). In six of these subjects, the apparent drug reactions were severe enough that the drugs were discontinued or the

dosages decreased. In contrast, only 6 (15 percent) of the 40 subjects who received atovaquone and azithromycin reported symptoms consistent with adverse drug reactions, and in 1 of them treatment was discontinued on the sixth day because of a hive-like rash (relative risk of an adverse reaction with clindamycin and quinine, 4.81; 95 percent confidence interval, 2.18 to 10.62; $P < 0.001$). Overall, adverse reactions were fewer and less severe in the subjects who received atovaquone and azithromycin than in those who received clindamycin and quinine.

Resolution of Symptoms

To compare the effects of atovaquone and azithromycin with those of clindamycin and quinine on the duration of symptoms, we determined the proportion of subjects in each treatment group whose symptoms resolved completely within one week and one, three, and six months after the beginning of treatment. Fever resolved within eight days after the start of treatment in all the subjects who received atovaquone and azithromycin and within seven days in all the subjects who received clindamycin and quinine. In more than half the subjects in each group, symptoms had resolved at three months (65 percent of the subjects in the atovaquone-and-azithromycin group and 73 percent of those in the clindamycin-and-quinine group, $P = 0.66$). In none of the subjects in either group did symptoms persist six months after the start of treatment. Persistent symptoms of babesiosis were severe enough in 4 of the 18 subjects who received clindamycin and quinine that they were admitted to the hospital after one or two days of treatment. Each then received a seven-day course of intravenous clindamycin and oral quinine. None of the subjects who received atovaquone and azithromycin were hospitalized after treatment was initiated. In general, symptoms of babesiosis resolved at least as rapidly in the subjects who received atovaquone and azithromycin as in those who received clindamycin and quinine.

Duration of *Bab. microti* Infection

We also analyzed the duration of *Bab. microti* infection in the subjects according to their assigned treatment. Regardless of the regimen, no piroplasms were discovered on microscopical examination more than 3 weeks after the start of therapy, and no *Bab. microti* DNA was identified after 12 weeks (Fig. 1). Because parasitemia may have persisted after the last positive findings on microscopical examination or PCR analysis, we also determined the amount of time that passed between the start of therapy and an examination at which no evidence of parasitemia could be detected. Again, parasitemia persisted for as long in the subjects who received atovaquone and azithromycin as in those who received clindamycin and quinine; no evidence of infection was detected 19 months

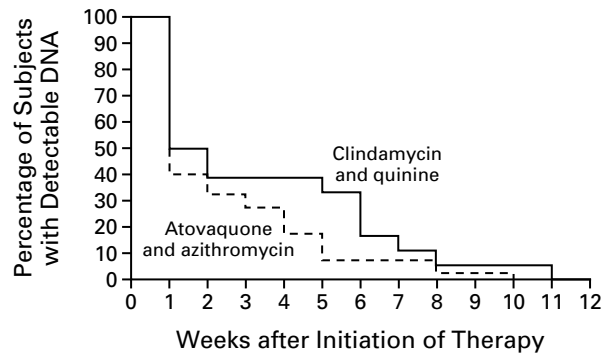


Figure 1. Persistence of DNA Detectable by PCR Amplification in the Blood of Patients with *Babesia microti* Infection Who Received a Seven-Day Regimen of Clindamycin and Quinine or Atovaquone and Azithromycin.

There was no significant difference in the duration of parasitemia between the 18 subjects treated with clindamycin and quinine and the 40 subjects treated with atovaquone and azithromycin ($P = 0.14$ by the log-rank test).

after the start of therapy. Thus, babesial infection was cleared as rapidly with an antibiotic regimen consisting of atovaquone and azithromycin as it was with a standard regimen of clindamycin and quinine.

DISCUSSION

Combined therapy with clindamycin and quinine, the current treatment of choice for human babesiosis, was first used in 1982 to treat a newborn infant who had become infected with *Bab. microti* from a blood transfusion.¹¹ Although this regimen is generally successful, adverse drug-related reactions are frequent, and infection occasionally persists.^{7,12,13} Of patients who receive clindamycin and quinine, about half have adverse effects,⁶ most frequently tinnitus, vertigo, or gastrointestinal upset.²⁴

In this study, ethical considerations required us to exclude subjects who had a babesial illness that was life-threatening, or who were 18 years of age or younger, and we limited the study to people with symptoms attributable to *Bab. microti* infection. These restrictions therefore limit the scope of any clinical recommendations that we can make on the basis of our results. The accepted standard of care should, of course, remain the treatment of choice for any groups of patients in whom a new regimen has not been evaluated. Hence, conventional therapy with clindamycin and quinine and exchange transfusion, when necessary, should be administered to patients with babesiosis that is life-threatening.

The use of atovaquone in combination with azithromycin as treatment for human babesiosis is based on the demonstrated efficacy of these drugs in treating malaria.^{15,16} This drug combination effectively elim-

inated *Bab. microti* parasitemia in hamsters,¹⁴ and it has been used successfully to treat a patient with human babesiosis after traditional therapy with clindamycin and quinine failed.²⁵ In hamsters, both atovaquone (a hydroxy-1,4-naphthoquinone) alone and azithromycin (an azalide macrolide) alone appeared to be effective. Neither should be used alone, however, because the combination of the two drugs was more effective than either one alone.¹⁴

Neither the regimen of atovaquone and azithromycin nor the regimen of clindamycin and quinine clears *Bab. microti* merozoites from the human blood as rapidly as might be desired. Clearance tends to be delayed and inconsistent, and in some cases blood-borne parasites may be present several months after treatment is completed. In the absence of therapy, however, *Bab. microti* parasitemia may persist for more than two years.⁷ In clinical practice, the duration of parasitemia may be difficult to monitor, because few patients are willing to submit to repeated blood sampling. Delayed clearance is consistent with previously reported data, thereby confirming the common observations that even with the use of specific therapy parasitic pathogens persist longer than do bacteria and that babesial parasitemia appears to be particularly resistant to antimicrobial therapy. With persistent infection, symptoms may be prolonged, the possibility of relapse remains, and a subsequent blood transfusion from the infected person may endanger the recipient.

The price paid by pharmacies for atovaquone and azithromycin is greater than that paid for clindamycin and quinine. However, institutions may find it economically favorable to choose atovaquone and azithromycin, because for many patients the regimen of clindamycin and quinine must be abandoned, with unused medication wasted as a result. In the long run, the issue of cost should not influence the choice between treatment with clindamycin and quinine and treatment with atovaquone and azithromycin.

Our observations indicate that an antibiotic regimen based on a combination of atovaquone and azithromycin is generally superior to one based on a combination of clindamycin and quinine for treatment of babesiosis, mainly because the former is better tolerated by patients. We therefore recommend that physicians consider the use of atovaquone and azithromycin for the treatment of non-life-threatening babesiosis in immunocompetent adult patients and in others who cannot tolerate clindamycin and quinine.

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