A CONTROLLED TRIAL OF A SINGLE DOSE OF AZITHROMYCIN FOR THE TREATMENT OF CHLAMYDIAL URETHRITIS AND CERVICITIS

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Abstract *Background.* Currently, there is no single-dose therapy that is effective in the treatment of urethral or endocervical infections with *Chlamydia trachomatis.* Azithromycin is a new azalide antibiotic that has substantial activity against *C. trachomatis,* is concentrated intracellularly, and has a long half-life in serum and tissue.

Methods. We conducted a trial in which 299 female patients and 158 male patients with uncomplicated genital infection and a positive *C. trachomatis* antigen test were randomly assigned to receive either azithromycin (1 g once orally) or doxycycline (100 mg orally twice daily for seven days). Only patients subsequently determined to have a culture positive for *C. trachomatis* at base line were included in the evaluation of efficacy.

Results. Among the patients who could be evaluated, 5 of the 141 patients (4 percent) treated with azithromycin did not respond to treatment, as compared with 3 of the 125 patients (2 percent) treated with doxycycline (difference between groups, 2 percent; 95 percent confidence interval, 0 to 6 percent). Of the patients evaluated 21 to 35 days after treatment, none of 112 treated with azithromycin and 1 of 102 treated with doxycycline had a positive culture. The rates of bacteriologic cure were similar for the 98 female patients (97 percent) and the 43 male patients (95 percent) treated with azithromycin. Seventeen percent of the patients who received azithromycin and 20 percent of those treated with doxycycline had mild-to-moderate drug-related side effects, mainly gastrointestinal symptoms.

Conclusions. A single 1-g dose of azithromycin is as effective for the treatment of uncomplicated genital chlamydial infections as a standard seven-day course of doxycycline. (N Engl J Med 1992;327:921-5.)

IN the United States, *Chlamydia trachomatis* is the most common sexually transmitted pathogen. Several million cases of chlamydial infection occur in the United States every year.[1]

C. trachomatis causes substantial morbidity in men, women, and infants. The most common presentations of chlamydial infection in sexually active adults are urethritis and cervicitis. Chlamydial infection is also responsible for many cases of epididymitis, endometritis, acute salpingitis, ectopic pregnancy, and obstructive infertility in women.[2,3] Infected pregnant women can also transmit the infection to their infants at birth, resulting in neonatal conjunctivitis and chlamydial pneumonia.[4]

The complex life cycle and relatively slow replication of *C. trachomatis* have important implications for therapy. Although single-dose regimens are available for the treatment of gonococcal infections, there are no such regimens for the treatment of uncomplicated chlamydial infection. Seven-day, multidose regimens of tetracycline, doxycycline, or erythromycin are the most frequently used treatments for genital chlamydial infections, but many patients do not complete the course of therapy.[5] The rate of noncompliance is particularly high among patients with asymptomatic infection.

Azithromycin is the prototype of a new group of antibiotics known as azalides. It differs structurally from the macrolide erythromycin by the insertion of a methyl-substituted nitrogen at position 9a in the lactone ring, creating a 15-membered ring structure. In vitro, azithromycin has good activity against *C. trachomatis*, with a minimal inhibitory concentration of 0.03 to 0.25 mg per liter.[6,7] Azithromycin also has good in vitro activity against other sexually transmitted pathogens, including *Ureaplasma urealyticum.*[8] More importantly, it has good bioavailability, with sustained high levels in tissue after a single oral dose. In a recent study,[9] tissue levels of 1.44 μg of azithromycin per gram were measured in tissue from the female genital tract 24 hours after a single 500-mg dose of the drug; the half-life in this tissue was 67 hours. This pharmacokinetic profile suggests that azithromycin may be effective after even a single dose.

We conducted a multicenter, randomized study to evaluate the efficacy and safety of a single 1-g dose of orally administered azithromycin and to compare its effects with those of the standard seven-day course of doxycycline (100 mg twice daily) for the treatment of chlamydial urethral infection in men and chlamydial urethral and endocervical infection in women.

METHODS

Patients

A total of 457 patients (158 male and 299 female) with presumptive chlamydial urethral or endocervical infection (or both) were enrolled at 21 centers in the United States. Study subjects who were at least 16 years of age were recruited from sexually transmitted disease, college-student health, adolescent health, and family-planning clinics. Patients considered to be at high risk for chlamydial infection were evaluated. Most had clinically evident urethritis or mucopurulent cervicitis, but some were asymptomatic sexual partners of patients with proved *C. trachomatis* infection. Since objective evidence of chlamydial infection was required before enrollment, the patients were screened with antigen tests that provided rapid results, and only the patients with positive results were enrolled.

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Some female patients were referred to us because of a positive chlamydial test on routine screening. The rapid screening tests used in the various clinical centers were the Microtrak direct monoclonal-fluorescent-antibody test (Syva, Palo Alto, Calif.), Testpack (Abbott Laboratories, Chicago), Kodak Surecell (Kodak, Rochester, N.Y.), and Clearview (Unipath, Mountain View, Calif.). Patients with Gram's stains of urethral or endocervical specimens suggesting infection with *Neisseria gonorrhoeae* were eligible if they also had a positive rapid screening test for *C. trachomatis*.

Patients were excluded from the study for the following reasons: evidence of gonococcal pharyngitis, proctitis, or disseminated gonococcal infection; treatment with a systemic antibiotic within 72 hours before enrollment; evidence of salpingitis or epididymitis; history of allergy or hypersensitivity to erythromycin or doxycycline; history of serious underlying chronic disease; a positive test for hepatitis B surface antigen; and known alcohol or drug abuse. Patients who were pregnant or lactating were also excluded. Before enrollment the patients gave written, informed consent. All the patients were examined before treatment, and the presence or absence of urethral and endocervical discharge was noted. In the female patients the presence or absence of cervical erythema, friability, edema, and hypertrophic ectopy was recorded.

Microbiologic Studies

To confirm the diagnosis of *C. trachomatis* infection, specimens for culture were obtained from the urethra in male patients and from the urethra and endocervix in female patients. McCoy cells grown in flat-bottomed vials or plastic plate wells were used as the culture medium. Otherwise, details of the culture method were not standardized between centers. The minimal concentration of azithromycin and doxycycline needed to inhibit *C. trachomatis* was measured for selected isolates with McCoy cells grown in the wells of flat-bottomed plastic plates as described elsewhere.[10] In addition, urethral, endocervical, pharyngeal, and rectal specimens were obtained and inoculated directly onto selective chocolate agar for the identification of *N. gonorrhoeae*.

Treatment

Patients were randomly assigned to receive either a single dose of 1 g of azithromycin (four 250-mg capsules) on day 1 or a dose of 100 mg of doxycycline (Vibramycin) (one capsule) twice daily for seven days. Placebos were not used. Therapy was initiated within 48 hours after the cultures were obtained. The drugs were taken orally at least one hour before or two hours after a meal. The drugs were distributed by a person who was not involved in the selection or evaluation of the patients. Patients with concomitant gonococcal infections were treated with a single 250-mg dose of ceftriaxone given intramuscularly either at the initial visit or at the first follow-up visit. Patients were instructed to use a condom if they had sexual intercourse during the study. The randomization table and antibiotics were provided by Pfizer Central Research (Groton, Conn.).

Evaluation of Treatment

Only patients with positive *C. trachomatis* cultures at base line were included in the analysis of clinical and bacteriologic outcome. Endocervical and urethral specimens were obtained during follow-up evaluations performed 5 to 11 days, 12 to 20 days, and 21 to 35 days after the initiation of treatment. At each evaluation, signs and symptoms of infection were assessed and patients were questioned about interim sexual exposure. Compliance with the doxycycline regimen was documented at the first follow-up visit by counting the number of pills remaining and reviewing the patient's history. Any patients who admitted having intercourse without a condom were excluded from further evaluation at that point, as were patients given additional antibiotics active against *C. trachomatis*. The clinical response to treatment was classified in the following manner, according to the investigator's final assessment: complete resolution of the signs and symptoms of infection (cure), incomplete resolution of the signs and symptoms (improvement), or no apparent response to the study drug or a worsening of the signs and symptoms (failure). The bacteriologic response was classified as either complete (cure), on the basis of a negative culture for *C. trachomatis* at follow-up, or incomplete (failure), on the basis of a positive chlamydial culture at follow-up.

All side effects that occurred during therapy or within 35 days of the end of treatment, reported by the patients or observed by the investigators, were recorded at each visit. The severity of each side effect was classified as mild, moderate, or severe. The data for all patients enrolled in the study were included in the assessment of side effects.

Blood and urine samples were obtained within 24 hours before treatment and at each follow-up visit. Standard hematologic, biochemical, and urinary analyses were performed to detect asymptomatic drug toxicity.

Statistical Analysis

All statistical tests were two-tailed. The distributions of the clinical response and rates of bacteriologic eradication were compared with the Cochran–Mantel–Haenszel method.

Results

Azithromycin was used to treat 237 patients (85 male and 152 female), and doxycycline was used in 220 patients (73 male and 147 female). The two groups were similar with respect to age, weight, and racial or ethnic distribution (Table 1). Eighty-three of the azithromycin-treated patients (35 percent) and 87 of the doxycycline-treated patients (40 percent) did not have a positive base-line *C. trachomatis* culture and were therefore excluded from the analysis of drug efficacy. Some of these negative base-line cultures can be accounted for by the long interval (one to two weeks) between the screening of asymptomatic female patients and the performance of the base-line culture. There may have been spontaneous cures or undisclosed antibiotic treatment in some cases. In addition, there was no quality control of the rapid screening tests used, which may have contributed to a higher-than-expected number of false positive results in this study. Finally, false negative culture results are expected in 10 to 15 percent of patients with chlamydial infections even under ideal conditions. An additional 13 azithromycin-treated patients and 8 doxycycline-treated patients were excluded because they did not return for any of the follow-up visits. Thus, a total of 141 azithromycin-treated patients and 125 doxycycline-treated patients were available for the analysis of bacteriologic efficacy. Eighty-seven percent of the patients had two or more follow-up visits. The bacteriologic results are summarized in Table 2. There were five (4 percent) treatment failures in the azithromycin group and three (2 percent) in the doxycycline group (difference in the failure rate, 2 percent; 95 percent confidence interval, 0 to 6 percent). Three of the patients who did not respond to azithromycin had positive cultures on the first follow-up visit, as did two of the patients who did not respond to doxycycline.

Cultures were obtained from 112 of the azithromycin-treated patients during the follow-up visits scheduled 21 to 35 days after enrollment (mean, 29 days

Table 1. Characteristics of the Patients in the Study.*

Characteristic	Azithromycin (N = 237)	Doxycycline (N = 220)
Sex (no.)		
Male	85	73
Female	152	147
Age (yr)		
Males		
Mean	25.2	24.9
Range	16–50	16–48
Females		
Mean	22.0	22.0
Range	16–42	16–46
Race or ethnic group (no.)		
White	82	77
Black	139	117
Hispanic	11	17
Other	4	8
Unknown	1	1
Weight (kg)		
Males		
Mean	74.9	76.0
Range	56–112	45–103
Females		
Mean	61.8	62.8
Range	45–100	43–132

*Eighty-three of the azithromycin-treated patients and 87 of the doxycycline-treated patients had negative cultures for *C. trachomatis* at base line and were therefore excluded from the analysis of drug efficacy.

after enrollment) and from 102 of the doxycycline-treated patients (at a mean of 29 days after enrollment). None of the azithromycin-treated patients and only one of the doxycycline-treated patients had positive cultures at this time. Ten patients in each group had concomitant *N. gonorrhoeae* infections and received ceftriaxone in addition to the assigned study drug. Both *N. gonorrhoeae* and *C. trachomatis* were eradicated in all these patients.

Isolates of *C. trachomatis* from 97 patients (49 from New Orleans, 21 from Indianapolis, and 27 from the other sites) were tested in vitro for susceptibility to azithromycin and doxycycline. The minimal concentrations of azithromycin needed to inhibit 50 percent and 90 percent of these isolates were 1 mg per liter and 2 mg per liter, respectively; the respective values for doxycycline were 0.125 mg per liter and 0.5 mg per liter. Two pretreatment isolates from a patient who did not respond to azithromycin were tested. The minimal inhibitory concentrations for these two isolates were well within the susceptible range for both azithromycin (0.5 and 1 mg per liter) and doxycycline (0.125 and 0.25 mg per liter).

Nineteen of the patients given azithromycin (15 female and 4 male) and 15 of the patients given doxycycline (9 female and 6 male) were asymptomatic and had no signs of infection at the base-line visit; therefore, the clinical responses of 122 azithromycin-treated patients (83 female and 39 male) and 110 doxycycline-treated patients (78 female and 32 male) could be evaluated at one or more follow-up visits. Among this group of patients, all the male patients had urethral discharge, dysuria, or both, and most of the women were asymptomatic but had one or more signs of endocervical inflammation, the most common of which was endocervical discharge. At the last follow-up visit, 97 percent of the male patients and 98 percent of the female patients had responded clinically to azithromycin, as compared with 91 percent of the male patients and 95 percent of the female patients treated with doxycycline (difference in rates of clinical improvement for male patients, 6 percent; 95 percent confidence interval, 0 to 17 percent; difference in clinical rates of improvement for female patients, 3 percent; 95 percent confidence interval, 0 to 9 percent).

Side effects considered by the investigators to be related to treatment were reported in 41 of 237 patients given azithromycin (17 percent) and in 43 of 220 patients given doxycycline (20 percent). Only one doxycycline-treated patient was withdrawn from treatment; this was due to nausea and vomiting. The most common treatment-related side effects in both groups involved the gastrointestinal tract (Table 3). Diarrhea was more common in azithromycin-treated patients, whereas nausea and vomiting were more common among those taking doxycycline. All side effects were judged to be of mild or moderate severity except one case of nausea in the azithromycin group and a photosensitivity reaction in the doxycycline group.

Abnormal laboratory-test results that may have been related to treatment were recorded in 17 azithromycin-treated patients (7 percent) and 6 doxycycline-treated patients (3 percent). Small increases in liver enzyme or serum bilirubin levels were observed in four

Table 2. Rates of Bacteriologic Cure for Each Follow-up Visit.

Length of Follow-up	Azithromycin (N = 141)	Doxycycline (N = 125)
	no. culture-negative/ no. with cultures (%)	
5–11 Days		
Females	87/89 (98)	76/77 (99)
Males	40/41 (98)	36/37 (97)
Total	127/130 (98)	112/114 (98)
12–20 Days*		
Females	78/79 (99)	70/70 (100)
Males	31/32 (97)	26/26 (100)
Total	109/111 (98)	96/96 (100)
21–35 Days*		
Females	78/78 (100)	72/73 (99)
Males	34/34 (100)	29/29 (100)
Total	112/112 (100)	101/102 (99)
Cumulative results†		
Females	95/98 (97)	85/87 (98)
Males	41/43 (95)	37/38 (97)
Total	136/141 (96)	122/125 (98)

*Patients with a positive culture at a previous follow-up are not included in the data for subsequent follow-up intervals. Some patients did not return for all three follow-up visits.

†Twelve patients given azithromycin and 13 given doxycycline were assessed only at the first follow-up visit (days 5 through 11). The 95 percent confidence interval for the 2 percent difference in bacteriologic cure rates between the treatment groups was 0 to 6 percent.

Table 3. Treatment-Related Side Effects in the Two Groups of Patients.*

Side Effect	Azithromycin (N = 237)	Doxycycline (N = 220)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	15 (6)	4 (2)
Nausea	13 (5)	24 (11)
Vomiting	5 (2)	13 (6)
Abdominal pain	9 (4)	3 (1)
Other	3 (1)	0
Skin rash	3 (1)	3 (1)
Neuropsychiatric	4 (2)	1 (0.5)
Other	5 (2)	4 (2)
Total†	41 (17)	43 (20)

*The odds ratios and 95 percent confidence intervals for the most common side effects were as follows: diarrhea — 3.6, 1.4 to 15.7; nausea — 0.5, 0.2 to 1.0; and vomiting — 0.3, 0.1 to 1.0.

†Some patients had more than one side effect.

patients in each group. Seven patients in the azithromycin group had small, transient decreases in the absolute neutrophil count.

Discussion

We found that a single 1-g dose of azithromycin is as effective as the standard seven-day doxycycline regimen in the treatment of *C. trachomatis* urethral or endocervical infection. One previous study also suggested that a single dose of azithromycin is an effective treatment for uncomplicated genital chlamydial infections.[11] Three azithromycin regimens, each delivering a total of 1 g, were compared with a seven-day course of doxycycline in which 100 mg of the drug was given twice daily for the treatment of sexually transmitted disease.[11] Four weeks after enrollment *C. trachomatis* had been eradicated in 43 of the 44 patients (98 percent) who received a single dose of azithromycin. The other two azithromycin regimens (in which a total of 1 g was given over a period of one or two days) were also effective.

Our study was designed primarily to determine the bacteriologic efficacy of azithromycin in the treatment of *C. trachomatis* infections. Clinical efficacy was assessed, but the criteria used to define urethritis and cervicitis were subjective (such as observable urethral or endocervical discharge). Bearing in mind these limitations, we nevertheless found that the rates of clinical failure among both male and female patients were very low. Although these data support the use of azithromycin for the treatment of urethritis caused by *C. trachomatis*, the efficacy of the drug for nonchlamydial nongonococcal urethritis has not been established. Azithromycin has good in vitro activity against *U. urealyticum*,[12,13] the other recognized pathogen in this disease.[14] Therefore, the drug should be effective for nongonococcal urethritis, but further studies are required to support this hypothesis.

The pharmacokinetic profile of azithromycin is characterized by sustained high concentrations in cells and tissues.[15,16] The high concentration of azithromycin in the intracellular compartment may be related to the amphophilic and dibasic nature of the azalide structure, resulting in a tendency to concentrate in subcellular compartments of low pH.[17] By contrast, tetracycline, doxycycline, and erythromycin do not produce sustained high concentrations in tissue, and multiple doses must be administered to maintain adequate intracellular drug levels.

Serum azithromycin concentrations are low; thus, a more accurate estimate of the in vivo efficacy of the drug in the treatment of intracellular pathogens such as *C. trachomatis* may be derived by an assessment of the minimal inhibitory concentrations in relation to the tissue concentrations of the antibiotic. The maximal levels of azithromycin in serum are only about 0.4 mg per liter after a 500-mg oral dose,[18] whereas tissue levels 24 hours after the same dose range from 3 to 6 mg per kilogram of body weight and remain above 1 mg per kilogram for several days. The minimal concentrations of azithromycin needed to inhibit 50 percent and 90 percent of *C. trachomatis* in this study were 1 mg per liter and 2 mg per liter, respectively, as compared with a minimal inhibitory concentration of 0.03 to 0.25 mg per liter in previous studies.[6,7] Thus, it appears likely that tissue levels are indeed the critical factor in determining the efficacy of azithromycin against intracellular pathogens such as *C. trachomatis*.

Though published studies consistently report high success rates after multiple-dose therapy for chlamydial infections, there has always been some doubt that treatment is as effective outside the research setting because of problems with compliance.[19,20] For this reason effective drug regimens that are easy to administer are preferred. The rate of compliance with a seven-day course of therapy is probably lowest among patients with asymptomatic chlamydial infections identified by routine screening programs or on the basis of an infection in their sexual partners. Unfortunately, these are the very patients who appear to be at greatest risk for the serious long-term sequelae caused by chlamydial infections. Chronic asymptomatic infection of the fallopian tubes may be the primary cause of tubal scarring, which is responsible for obstructive infertility and ectopic pregnancy.[2,3,21] Asymptomatic men probably play a major role in the dissemination of the organism and, in part, account for its high prevalence in the population.[22] Single-dose therapy, as is available for early stages of syphilis and gonorrhea, would be ideal for the treatment of chlamydial infections, since it would ensure a 100 percent rate of compliance.

Preliminary analyses indicate an efficacy of approximately 85 to 95 percent for a single 1-g dose of azithromycin in the treatment of gonorrhea. A 2-g dose is more effective, but significantly increases the incidence of mild-to-moderate gastrointestinal side effects (Pfizer Central Research: unpublished data). Therefore, it appears that the 1-g dose of azithromycin should be combined with a more effective antigonococcal drug to treat patients infected with

both *N. gonorrhoeae* and *C. trachomatis*. Further studies are needed to establish the efficacy of a single dose of azithromycin for salpingitis and epididymitis caused by *C. trachomatis*. Effective single-dose therapy may improve efforts to limit the spread of this important sexually transmitted organism.

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Appendix

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