

## COMPARATIVE STUDY OF AZITHROMYCIN VERSUS DOXYCYCLINE FOR TREATMENT OF EARLY *LYME BORRELIOSIS*

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**Data from European and American authors concerning azithromycin efficacy in the treatment of Lyme borreliosis appear controversial. The aim of this study is to establish whether azithromycin is applicable to patients with early Lyme borreliosis.**

In these studies a total of 93 patients with clinically defined erythema migrans were enrolled. Forty-nine of them were treated with doxycycline for 14 days and forty-four received azithromycin for 5 days. Physical examinations and serologic investigations by ELISA and Western blot for positive findings were performed at the first visit and repeated 4-6 weeks, 3, 6, and 12 months after starting treatment.

Complete resolution of erythema migrans within 14 days after the start of therapy was found in 42 (85,7%) of 49 doxycycline-treated and in 39 (88,6%) of 44 azithromycin-treated patients. Incomplete resolution of erythema migrans and/or persistence of minor symptoms (post-Lyme syndrome) for at least 3 months were detected in 6 (12,2%) of doxycycline-treated and in 4 (9,1%) of azithromycin-treated patients. One patient in each group (2% vs. 2,3%) showed progression of the disease with later manifestations of Lyme borreliosis.

Compared to doxycycline, azithromycin possessed equal efficacy for treatment of early Lyme borreliosis. There was no difference in clinical outcome between the two treatment regimens.

Lyme borreliosis is the most commonly reported tick-borne disease in the Northern hemisphere (1). The disease affects mainly skin, nervous system, joints, and heart. Three separate stages in the clinical development of the disease could be distinguished – early localized, early disseminated, and late Lyme borreliosis. Except erythema migrans (EM), the clinical hallmark of early localized Lyme borreliosis, disease expressions are not specific and need laboratory confirmation. Routine laboratory diagnosis of Lyme borreliosis is serological and according to the two-step approach, a sensitive ELISA or IFA test is recommended as a first step and immunoblot as a second step to confirm positive and borderline results from the first assay.

Clinical effectiveness of antibiotic treatment

decreases markedly with the progression of the disease. Therefore, early diagnosis and treatment are of great importance. Standard antibiotic treatment of early Lyme borreliosis includes 14-day course of doxycycline (2). In vitro studies have shown antiborrelial activity of azithromycin. Clinical trials in Europe and the USA have revealed controversial results for the efficacy of 5-day azithromycin in the treatment of early Lyme borreliosis (3,4).

The objectives of this study were to compare clinical outcome in patients with erythema migrans treated with standard 14-day doxycycline and with 5-day azithromycin and to establish the suitability of 5-day azithromycin to Bulgarian patients with early Lyme borreliosis.

*Key words: Lyme borreliosis, Borrelia burgdorferi, erythema migrans, antibiotic treatment, doxycycline, azithromycin*

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## MATERIALS AND METHODS

### Patients

A total of 93 patients with physician diagnosed erythema migrans were included in the study. Pregnant patients and children, younger than 8 years, were excluded from the study as well as those with adverse reactions to tetracyclines and azithromycin.

### Treatment

Patients were randomly assigned to receive either doxycycline (Doxycyclin, Balkanpharma) or azithromycin (Azatril, Balkanpharma). Forty-nine patients were treated with doxycycline 100 mg twice daily for 14 days and 44 patients received azithromycin 500 mg twice daily for the first day, followed by 500 mg once daily for the next four days.

### Follow-up

Physical examination, clinical evaluation, serologic assessment (ELISA and Western blot for positives) were repeated 4-6 weeks, then 3, 6, and 12 months after starting the treatment.

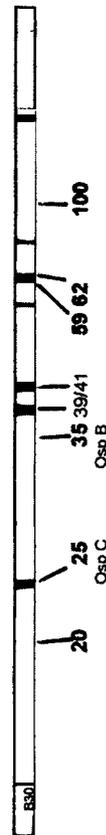
### Evaluation of the clinical response

Clinical response was evaluated on the basis of the EM resolution and eventual onset of manifestations, associated with Lyme borreliosis. Three different categories were used:

- 1) Complete resolution of erythema migrans and concomitant minor complaints and absence of Lyme borreliosis manifestations during follow-up period;
- 2) Incomplete resolution of erythema migrans and/or persistence of concomitant minor symptoms with improvement during follow-up;
- 3) Progression of the disease and onset of the clinical manifestations of early disseminated or late Lyme borreliosis.

## RESULTS

Forty-nine patients received doxycycline and forty-four patients were treated with azithromycin. All study patients showed one erythema migrans lesion. The two treatment groups were similar with respect to: mean age, mean diameter of the lesions, duration of the disease and manifestation of systemic symptoms (headache, fatigue, arthralgia, myalgia). The duration of erythema migrans before

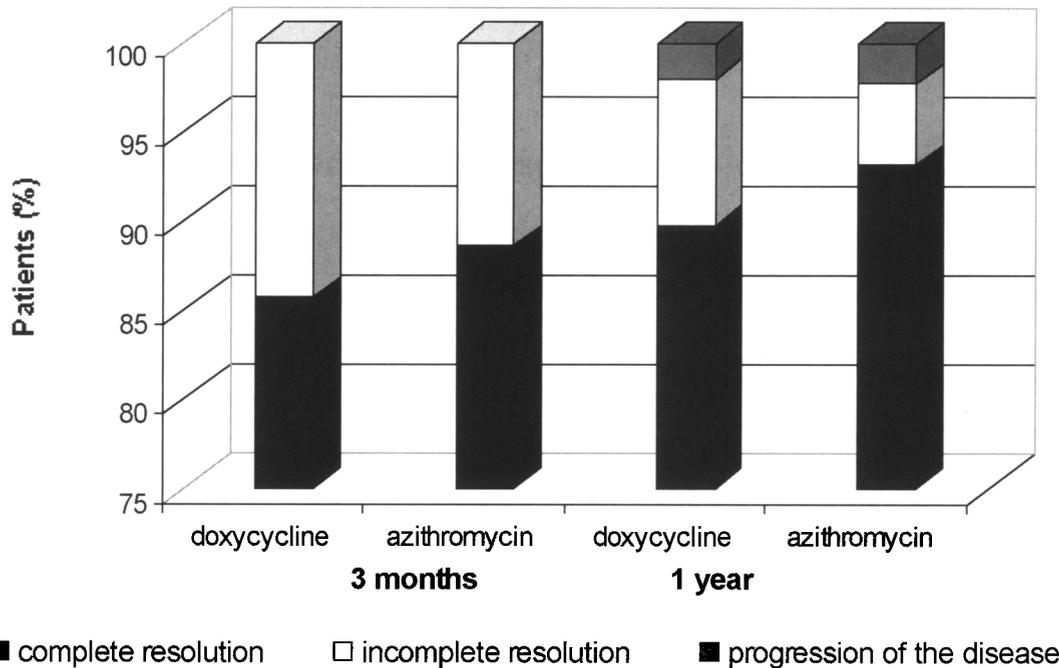


**Fig. 1.** Immunoblots were interpreted as positive when at least 2 clear intensive bands from highly specific antigen bands (p100 kDa; p59/p62 kDa; p41/p39 kDa - flagellin; p35 kDa - OspB; p25 kDa - OspC; p20 kDa) are presented.

treatment was 7,3 days for the first group and 8,2 days for the second group (non-significant difference) (Tab. I). Diagnosis was confirmed serologically in 42 (45,2%) of 93 study patients (Fig.1).

Complete resolution of erythema migrans within 14 days after the start of therapy was found in 42 (85,7%) of 49 doxycycline-treated and in 39 (88,6%) of 44 azithromycin-treated patients. Three months after starting treatment, the rest of the patients: seven patients (14,3%) of doxycycline and five (11,4%) of azithromycin group showed improvement despite incomplete resolution of erythema migrans and/or persistence of minor symptoms (Fig.2). Eleven (22,4%) of doxycycline group and 9 (20,5%) of azithromycin group were still serologically positive.

At the end of the study period (12 months), 5 (10,2%) of doxycycline group and 4 (9,1%) of azithromycin group were still serologically positive. Overall 4 (8,2%) of doxycycline group and 2



**Fig. 2.** Clinical evaluation of azithromycin versus doxycycline. Clinical outcome 3 months after treatment is presented by columns 1 and 2, and after 1 year by columns 2 and 4. Columns 1 and 3 - doxycycline patients, columns 2 and 4 - azithromycin patients. Complete resolution is interpreted when erythema migrans and/or minor complaints resolved during the follow-up period. Resolution was interpreted as incomplete when erythema migrans is resolved incompletely or minor symptoms persisted. Progression of the disease appeared in case of onset of clinical manifestations of early disseminated or late Lyme borreliosis.

**Tab. I.** Demographic and clinical pre-treatment characteristics of erythema migrans patients.

Characteristic	Doxycycline	Azithromycin
Mean age (years)	42,3	46,6
Mean diameter of lesion (cm)	6,5	5,3
Duration of the disease before treatment (days)	7,3	8,2
Manifestation of systemic symptoms (number of patients and percentage)	17 (34,7%)	16 (36,4%)

(4,5%) of azithromycin group still showed minor symptoms. One patient in each group (2% vs 2,3%) developed major later manifestations of Lyme borreliosis with involvement of joints and heart resp. (Fig.2).

A drug-related adverse effect (gastrointestinal discomfort) was noted in 5 (10,2%) of doxycycline group and in none of azithromycin group.

**DISCUSSION**

Antibiotic susceptibility of *Borrelia burgdorferi* has been defined using various methods based on evaluation of minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC). It has been established that azithromycin had lower MIC and MBC values than tetracycline and doxycycline (5-7). In addition, azithromycin has shown to be more effective than clarithromycin and roxythromycin in experimental animal infection (8).

However, according to American authors, azithromycin is not now recommended as first-line therapy of early Lyme borreliosis (2) since

treatment with azithromycin shows worse results than treatment with doxycycline (4), despite earlier observations about azithromycin effectiveness (9).

Conversely, a number of European studies have revealed azithromycin efficacy (3,10-14). Strle et al. (10-12) and Barsic et al. (3) demonstrated faster resolution of local and systemic symptoms in patients treated with azithromycin when compared with those treated with doxycycline. Azithromycin and phenoxymethylpenicillin were equally effective in treatment of children with solitary erythema migrans and had comparable side effects (13-14).

This study was intended to compare clinical outcome in patients with erythema migrans treated with azithromycin and doxycycline. Resolution / persistence of erythema migrans and minor concomitant symptoms, the onset of new minor or major manifestations of Lyme borreliosis, and drug-related adverse effects, were recorded up to 12 months after the treatment.

Both antimicrobial agents lead to fast complete resolution of erythema migrans in similar percentages of patients. Headache, fatigue, arthralgia, and myalgia were the most common symptoms that persisted in both groups of the patients with differences being non-significant. Similar percentages of patients in each group developed manifestations of late Lyme borreliosis.

We found doxycycline to be associated with significantly higher percentage of drug-related adverse effects compared with azithromycin. Furthermore, doxycycline had longer treatment regimen (14-day vs. 5-day).

Our study confirmed results of some European authors of azithromycin efficacy (3,10-14) and was in discordance with data from american authors, showing worse results (4). In conclusion, our findings showed that azithromycin was as effective as doxycycline in the treatment of erythema migrans. Azithromycin could be safely and effectively used in the treatment of early Lyme borreliosis.

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