MINOCYCLINE IN EARLY LYME BORRELIOSIS

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ABSTRACT

The present study was performed to assess the efficacy of minocycline in the treatment of early Lyme Borreliosis. 126 patients with erythema migrans were included from June 1993 to April 1995 at the Department of Dermatology in Graz, Austria. The patients were treated with minocycline 100 mg b.i.d. orally for 14 days and clinically reexamined for 15 months on the average (1 - 30 months). Moreover, a punch biopsy from the erythema migrans lesion was taken in 78/126 patients to perform *Borrelia burgdorferi*-specific PCR analysis before treatment. A second punch biopsy adjacent to the first biopsy site was able to be obtained in 41/78 patients at the end of therapy. *Borrelia burgdorferi*-specific PCR yielded positive results in 71% of the patients before therapy. After minocycline treatment, *Borrelia burgdorferi*-specific gene segments were no longer detectable in any of the skin biopsy samples. The good clinical response in conjunction with the PCR data presented indicate the efficacy of minocycline for the treatment of early Lyme Borreliosis. Minocycline is the first antibiotic to be assessed on the molecular level in this indication.

KEY WORDS

erythema migrans, Borrelia burgdorferi, antibiotic therapy, minocycline, polymerase chain reaction (PCR)

INTRODUCTION

Various antibiotics have been shown to be effective in the treatment of erythema migrans (EM), the typical cutaneous manifestation of early Lyme Borreliosis (LB). Tetracyclines (1-14), beta-lactams (1-3,5-8,10-12,14-17) and macrolide antibiotics (1,2,4, 5,8,12,17) have been applied. However, none of the hitherto used antibiotics is considered universally effective and, till now, the optimal antimicrobial regimen has not been established. Minocycline, a second generation tetracycline with superior properties suitable for LB treatment, was first employed in EM patients by Weber et al. (18), but has not yet been examined in a series consisting of many patients. In a recent study on 14 EM patients from the Department of Dermatology in Graz, Austria, the efficacy of minocycline (100 mg b.i.d. orally for 14 days) was assessed by clinical and molecular parameters (19). In none of these 14 patients *Borrelia burgdorferi* (*Bb*)-specific DNA could be found in skin biopsy specimens after treatment in comparison to a positivity rate of 57% before therapy. The PCR results were in accordance with the good clinical outcome of the

patients. However, there were two drawbacks to this study, namely the small number of patients and the short follow-up period. Therefore, a long term follow-up study was carried out, including a total of 126 EM patients. All patients were treated with minocycline under the same regimen (100 mg b.i.d. orally for 14 days). The mean follow-up period for this examination was 15 months (ranging 1 to 30 months). Besides the clinical assessment, 41/126 patients were reassessed on the molecular level.

PATIENTS & METHODS

One hundred and twenty-six consecutive patients (m:f = 55:71, mean age 53 years) with EM were seen from June 1993 to April 1995 at the Department of Dermatology in Graz, Austria. The diagnosis was made on clinical and partly (78/126 patients) histopathologic grounds. Sixty-four of the 126 patients (51%) presented with the annular type of EM, 5 patients (4%) had a bull's eye type of EM. Fifty-two patients (41%) presented with a macular type of EM. Five patients (4%) had multiple EM lesions. The mean time of EM before the first hospital presentation was 16.5 days. Fifty of the 126 patients (40%) were classified as suffering from early disseminated LB owing to additional signs and symptoms (e.g. cephalea, fever, fatigue, myalgias, arthralgias, regional lymphadenopathy) or multiple EM lesions. All patients resided in a geographic area endemic for LB (Styria, Austria).

Besides the clinical examination at the first hospital visit (day 1), a 4 mm punch biopsy from the EM lesion was obtained in 78/126 patients under sterile conditions. These specimens were analyzed by PCR for the presence of *Bb*-specific DNA as described (20). In addition, patients were tested for specific serum IgG and IgM antibodies to *Bb*. Purified native flagella of *Bb*, strain DK-1, isolated from a human EM lesion (Dakopatts ELISA Kit, Dako Diagnostika, Glostrup, Denmark) was used as a test antigen (21).

All 126 patients were first reexamined at the end (day 8 - 14) of minocycline therapy (100 mg b.i.d. orally for 14 days). The first reevaluation was accompanied by a second 4 mm punch biopsy adjacent to the previous biopsy site in 41 of those 78 patients in whom a punch biopsy was obtained before therapy. Further clinical and serologic reevaluations took place for a minimum of one to a maximum of 30 months (mean time 15 months) after initiation of therapy (at months 1, 3, 6, 12, 18 and 30). Seven of the 126 patients were followed only until month 1, 10 patients until month 3, 25 patients until month 6, 40 patients until month 12, 29 patients until month 18, and 15 patients until month 30, respectively.

RESULTS

On first reevaluation (day 8 - 14), EM had disappeared completely in 50/126 patients (40%) and had faded and diminished in 70/126 patients (55%). Only in 6/126 patients (5%) erythema remained unchanged. On second reevaluation (month 1), residual erythema was still present in 21/126 patients (17%), and on third reevaluation (month 3) in 6/119 patients (5%), respectively. However, erythema showed a clear decrease in these patients at second and third reevaluation. On further reevaluations (months 6, 12, 18, 30), EM could no longer be detected in any patient. The mean duration of EM after initiation of treatment was 24 days in all 126 patients (ranging 4 - 122 days). Relapse of EM (i.e. reappearance at the site of the original lesion) could not be observed in any patient.

On first reevaluation (day 8 - 14), additional signs and symptoms were still present in 27 of those 50 patients (54%) who initially had extracutaneous features of the disease. Nine additional patients (7%) developed such problems („later sequelae") only between two and six months after therapy. Primary extracutaneous features and later sequelae, respectively, were present for a minimum of 3 days to a maximum of 36 days in all patients (mean time 7 days). All extracutaneous signs and symptoms were of minor importance according to the classification set forth by Steere et al. (22). Retreatment was not necessary in any patient.

PCR amplification of *Bb*-specific DNA from biopsy specimens of lesional skin, obtained prior to initiation of treatment (day 1), was successful in 55/78 patients (sensitivity 71%). Anamnestic and clinical data of these PCR-positive patients were similar to those of the 23 PCR-negative patients. *Bb*-specific gene segments could not be amplified by PCR in any of the 41 patients who underwent a second punch biopsy on first reevaluation (day 8-14).

At the time of the first hospital visit (day 1), 35/126 patients (28%) had a serum IgG antibody response to *Bb*, whereas only 13/126 patients (10%) had an IgM response.

On first reevaluation (day 8-14), serum *Bb* IgG antibodies could be found in 40/126 patients (32%),

IgM antibodies were detected in 32/126 patients (25%). There was no significant rise of antibody titres or persistence at high levels for longer than 6 months in any of the patients (data not shown).

Side effects of minocycline therapy were observed in 75/126 patients (60%): vertigo/dizziness in 52%, gastrointestinal irritation including diarrhea in 50%, nausea in 40%, cephalea in 25%, vomiting in 15% and candidal vaginitis in 5% of all patients. 2/126 patients (2%) ceased therapy because of vertigo. A Jarisch-Herxheimer reaction occurred in 3/126 patients (2%).

DISCUSSION

Adequate antibiotic therapy of all stages of LB is essential for curing the disease and preventing late sequelae (1). It was pointed out in previous reports that various antibiotics can be successfully administered in EM, including tetracycline (1-3,8-10,13), doxycycline (4-7,11-14), minocycline (18,19,23,39), penicillin (1,3,5,8,10,15-17), amoxicillin (7,11,12,15), ceftriaxone (16), cefuroxime (6,14), erythromycin (1,2,8) and azithromycin (4,5,12,17). However, treatment failures with the above-mentioned antibiotics are not uncommon (24-26), and a final recommendation for the treatment of EM does not yet exist.

Minocycline to which *Bb* has been shown to be very susceptible in vitro (27-29) has potential advantages for the treatment of borrelial infections in comparison to other antimicrobial agents: (i) Adequate antibiotic levels must be maintained for a long period of time to eliminate *Bb* (30). Minocycline has a serum half-life of single doses between 12 and 16 hours (31-34), thus providing effective drug levels. (ii) *Bb* can invade the central nervous system early in the course of LB (35). Therefore, the antibiotic drug employed for the treatment of EM should penetrate the blood brain barrier well. This requirement is fulfilled more sufficiently by minocycline than by all other antimicrobial agents used for EM therapy (31,32,36). (iii) Phototoxicity with the use of tetracyclines is well known. However, minocycline seems to be largely free of this problem (33,37,38) which is advantageous as the incidence of EM is highest in summer.

Only few reports exist on the application of minocycline in early LB which was first effectively administered in 11 patients with EM by Weber et al. (18). In a further study, Weber et al. were unable to find minocycline (100 mg b.i.d. orally for 14 days) superior to oral penicillin based on clinical outcome criteria in a non-randomized open study on 65 patients with early LB (39). Breier and colleagues performed another comparative study with minocycline (100 mg orally b.i.d. for 14 days) versus oral penicillin in 39 patients with EM (23).

No differences were found between these two antibiotics in terms of clinical and serologic parameters. Besides these studies, only case reports deal with the successful use of minocycline in EM (3,40,41). On the other hand, single treatment failures have been described so far with minocycline (26,42). In a pilot study the efficacy of minocycline (100 mg b.i.d. orally for 14 days) in 14 EM patients from the Department of Dermatology in Graz, Austria was examined on clinical and molecular grounds (19). In none of these 14 patients, *Bb*-specific PCR from skin biopsy samples yielded a positive result after therapy, whereas *Bb*-specific gene segments could be detected in 8/14 (57%) specimens from lesional skin before therapy. The PCR results were in accordance with the favourable clinical response from all 14 patients. Despite the two disadvantages of this study (small number of patients, short follow-up period of 10 weeks), it was the first one to assess antibiotic treatment in dermatoborreliosis on the molecular level.

One cause to assume a treatment failure in LB patients is the persistence of *Bb* (culture or PCR positivity after therapy) (42). Single positive culture results after therapy were already reported with the use of penicillin V (16), penicillin G (43), ceftriaxone (43), doxycycline (43), and azithromycin (17). Culture of *Bb* from (lesional) skin, however, is not highly sensitive and thus yields results not reliable enough for the assessment of antibiotic therapy. The advantage of PCR for this purpose is the capability to detect very low numbers of *Bb* organisms from various clinical sources.

Besides our pilot project (19), there is only one report on PCR examination of EM skin biopsies so far which also includes data on patients who had already received antibiotics (44). However, this prior antibiotic treatment consisted of only few doses of various antibiotics in 9 of a total of 44 patients with EM. The sensitivity of the *Bb*-specific PCR was 59% (22/35 untreated patients) to 62% (13/21 untreated patients) based on either a clinical or cultural diagnosis of the initial rash.

Of the 9 patients already treated antibiotically at the time of biopsy, two (22%) were positive by PCR analysis (one patient had received one dose of amoxicillin and the second five doses of tetracycline).

In our study, PCR assay succeeded in amplifying *Bb*-specific DNA in 55/78 patients (71%) from whom a pre-treatment biopsy specimen of lesional skin was obtained. At the end of minocycline therapy (day 8 - 14), however, PCR analysis disclosed no *Bb*-specific DNA in any of the 41 patients who had a post-treatment biopsy. The mean duration of EM was 24 days (ranging 4 - 122 days) after the start of therapy in 126 patients, no relapse of EM could be observed. Extracutaneous signs and symptoms lasted for a mean time of 7 days (ranging 3 - 36 days) in 59 patients, 9 of whom developed these associated problems after the end of therapy for the first time („later sequelae"). All of these additional signs and symptoms were of minor character.

Bb appears to be rapidly eliminated from the site of infection by minocycline. However, persisting extracutaneous infection with *Bb* cannot be absolutely excluded from the presented data. The clinical and serological outcome in our patients during an observation period of up to 30 months was excellent following the criteria recently reviewed by Weber (i.e. persistence or recurrence of EM, persistence and/or development of extracutaneous sequelae, significant increase or persistence of antibody titres to *Bb*) (42). Resolution time of EM in our patients was comparable with the data from other studies (45). Only 6/126 patients had EM lesions lasting longer than 90 days after the initiation of therapy (beyond reevaluation at month 3). Persistence of EM over such a relatively long period of time suggests a treatment failure. On the other hand, serological and molecular data speak against a treatment failure in these 6 patients who were free of associated symptoms of LB during the whole follow-up course. Moreover, it is well known that EM may sometimes persist up to 20 weeks or longer despite antimicrobial therapy (45).

The favourable outcome concerning extracutaneous signs and symptoms in our patients was not unexpected as they all suffered from only few and minor associated problems. Only 9/126 patients were suspected of suffering from „later sequelae" which were defined as signs and symptoms exceeding a duration of 3 weeks after initiation of therapy or as a new appearance of such symptoms after therapy (42). Major sequelae which always indicate a treatment failure and have been described in approximately 2% of patients in former studies (42) were not observed at all in our series.

The high rate of 60% with adverse effects (vertigo/dizziness, gastrointestinal irritation, nausea, cephalea, vomiting and candidal vaginitis) observed in our patients is likely to result from the dosage of 100 mg of minocycline twice daily. Symptoms such as vertigo and dizziness pointing to vestibular dysfunction were the leading side effects in the present study (52% of all patients). They are known to be common in minocycline therapy and occur to a greater frequency than with the use of other tetracyclines (33,46). These adverse events which subside after discontinuation of therapy may be an indicator for the good penetration of the blood brain barrier by the drug. Vertigo is rarer with the sustained release preparation (41) which is, however, not available in Austria. Since side effects are known to be dose dependent, it is worthwhile to examine whether a lower dose of minocycline (100 mg once daily) would have the same effect in treating EM without the inconvenient adverse events.

In summary, the good clinical outcome in a consecutive series of 126 EM patients over a follow-up period of up to 30 months in conjunction with the PCR data presented, indicates the efficacy of minocycline in the treatment of early LB.

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