CONCISE REPORT

Comparing 10-day and 4-month doxycycline courses for treatment of *Chlamydia trachomatis*-reactive arthritis: a prospective, double-blind trial

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Objective: To compare the efficacy of a 10-day and a 4-month doxycylcine course for the treatment of *Chlamydia trachomatis*-reactive arthritis (Ct-ReA).

Methods: Patients with active Ct-ReA were enrolled in a prospective, multicentre, double-blind, controlled clinical trial and randomised to receive doxycycline 100 mg twice daily for 10 days followed either by placebo or by continued doxycycline 100 mg twice daily over 4 months. Various clinical and laboratory parameters referring to disease activity were recorded in the beginning and at the end of treatment.

Results: 32 of 37 patients included (15 men and 17 women; mean (standard deviation) disease duration 17 (13) months completed the study; 17 were randomised to short-term doxycycline and placebo (placebo group) and 15 to prolonged treatment with doxycycline (doxycycline group) over the 4-month study period. After this time, only two patients from each group went into remission. There were no drop-outs owing to adverse events or treatment failures.

Conclusions: The results of this study suggest that prolonged treatment with a 4-month course of doxycycline is not superior to short-term treatment over 10 days in patients with Ct-ReA.

Reactive arthritis is defined as inflammatory joint disease caused by bacterial infection of the urogenital, gastrointestinal or upper respiratory tracts.[1] Despite a favourable prognosis in most patients with reactive arthritis, as many as one third of the patients have a chronic or relapsing course of the disease.[2] Although the causative microorganism cannot be cultured from the joint, intra-articular demonstration of bacterial antigens and nucleic acids suggests that the bacteria or bacterial fragments reach the joint and, in the case of chlamydia, persist in an aberrant but metabolically active form.[3] Furthermore, the causative extra-articular infection is often still present when arthritis develops.[4] Thus, antimicrobial agents represent a potential aetiologically oriented approach to treat reactive arthritis.[5]

Chlamydia trachomatis has emerged as the major cause of reactive arthritis.[6] Short-term antibiotic treatment is effective in treating genitourinary infection with *C trachomatis*, reduces the risk of developing subsequent arthritis, and is thought to prevent recurrent attacks of reactive arthritis.[7] However, when reactive arthritis has established, short courses of antibiotics seem to be ineffective in altering the course of the arthritis.[8] For long-term antibiotic treatment, only one publication suggested positive results in a controlled trial,[9] whereas other studies did not show an effect of prolonged treatment with an antibiotic on the course of the arthritis.[10 11] On the basis of the hypothesis that prolonged treatment with doxycycline eventually eradicates intra-articularly persisting chlamydiae, we conducted a randomised, double-blind, placebo-controlled study to compare the efficacy and safety of prolonged with standard short-term antibiotic course with doxycycline for the treatment of *C trachomatis*-reactive arthritis (Ct-ReA).

METHODS

Study design

The study was a randomised, double-blind, placebo-controlled trial conducted in two rheumatological centres—namely, Hannover Medical School, Hannover, Germany, and the rheumatological clinic in Bad Nenndorf, Schaumburg, Lower Saxony, Germany. In total, 37 patients gave informed consent and participated in this trial.

Criteria for patient selection

Between 1990 and 1994, adult outpatients or inpatients (aged between 18 and 65 years) presenting the first time and diagnosed with active Ct-ReA at the Department of Rheumatology, Hannover Medical School and at the rheumatological clinic in Bad Nenndorf were eligible to participate in this study. Case definition included at least one tender and swollen joint—not explained by another defined rheumatic disease—and evidence of urogenital infection with *C trachomatis* by either of the following two criteria: (1) detection of *Chlamydia*-specific antigen using immunofluorescence in genitourinary smears or first-void urine samples and (2) clinical symptoms of urogenital chlamydial infection at the time of developing arthritis, and raised anti-chlamydial antibodies in the serum (immunoglobulin (Ig)A $\geqslant$1:16 and IgG = 1:64). Patients known to have doxycycline or tetracycline intolerance, as well as pregnant women, were excluded from the study. There were no predefined limits regarding disease duration.

Drug administration

None of the patients had received antibiotics to treat the *C trachomatis* urogenital infection or the Ct-ReA before inclusion in the study. During the study, patients were given 100 mg doxycycline (Vibramycin, Pfizer, Karlsruhe, Germany) or identical placebo capsules (Pfizer) twice daily for 4 months. Each patient received a continuous number of capsules, which was randomly assigned (in blocks of 10) to either of the treatment arms. All patients and their sexual partners received a 10-day doxycycline course (100 mg twice daily) before the double-blind, placebo-controlled part of the study.

Abbreviations: Ct-ReA, *Chlamydia trachomatis*-reactive arthritis; ESR, erythrocyte sedimentation rate

Table 1 Characteristics of 32 patients with *Chlamydia trachomatis*-reactive arthritis at study entry before receiving short-term or long-term treatment with doxycycline

	Placebo group (n = 17) 10 days doxycycline	Doxycycline group (n = 15) 4 months doxycycline	p Value
Mean (SD) age, years	40.5 (12.1)	42.6 (13.7)	NS
Sex (female)	8/17 (47)	9/15 (60)	NS
Duration (range) of disease	16.0 (5–49)	17.1 (2–42)	NS
History of urogenital infection (months)	10 (59)	8 (53)	NS
Urogenital detection of *Chlamydia*	12 (71)	11 (73)	NS
IgG antibodies to *Chlamydia*	17 (100)	14 (93)	NS
IgA antibodies to *Chlamydia*	11 (65)	12 (80)	NS
Inflammatory lower back pain	4/11 (36)	7/14 (50)	NS
Enthesiopathy	2/11 (15)	4/13 (31)	NS
HLA-B27 positive	8/15 (53)	3/9 (33)	NS

HLA, human leucocyte antigen; NS, not significant.
Values are n (%) unless otherwise stated.

Concomitant drugs

Premedication or comedication with disease-modifying drugs, systemic or intra-articular corticosteroids 2 weeks before the baseline and during the study period was not permitted. The dosage of non-steroidal anti-inflammatory drugs during the study was stable or could be decreased; an increase of the dosage was not permitted.

Clinical evaluation

Demographic data included sex, age, duration of disease and history of urogenital infection. At the beginning and the end of the study, patients were clinically evaluated. Clinical data included patient's global assessment and intensity of pain (visual analogue scales), as well as duration of morning stiffness and fatigue (measured in min). The parameters collected by clinical examination were the number of tender joints and number of swollen joints.

Laboratory evaluation

Before study entry, first-void urine samples or genitourinary smears of the cervix and urethra in women and urethral smears in men were taken (Mikrotrak test, Syva, Palo Alto, California, USA). Urethral smears were considered to be positive if >7 inclusion bodies were identified. At the beginning and at the end of the trial, erythrocyte sedimentation rate (ESR), C reactive protein level and IgA/IgG-antibody titre to *C trachomatis* (Ipazym test, Medac, Hamburg, Germany) were measured. Human leucocyte antigen-B27 typing was available in only 24 of the 32 patients.

Statistical analysis

The predefined primary parameter for efficacy was remission of arthritis as defined by the preliminary American College of Rheumatology criteria for rheumatoid arthritis.[12] These criteria of remission, although neither specific nor validated for reactive arthritis, were chosen to measure the intended therapeutic goal. The sample size calculation indicated 16 patients per group under the following assumptions: rate of spontaneous remission not >25% in patients with >6 months disease duration, rate of prolonged antibiotic treatment at least 75%, α-error 0.05 and statistical power 80%.

Important secondary parameters for efficacy included ESR, C reactive protein, number of tender joints, number of swollen joints, intensity of pain and patient's global assessment.

Data were analysed by SPSS for MS Windows Release 6.0. Both groups were tested at the start of the trial for possible differences by the χ^2 test (with Yate's correction), Fisher's exact test or t test for unmatched pairs for comparison of means if variables showed normal distribution; otherwise the Mann–Whitney U test was used. The course of disease was evaluated separately in each treatment group, comparing means from the beginning and the end of the study using the t test for matched pairs and Mann–Whitney U test. A comparison between both study arms regarding the outcome of each parameter was carried out using a t test for unmatched pairs analysing mean differences in the course of disease. A value of $p<0.05$ was considered to be significant. Bonferroni adjustment for multiple testing was used when calculating the data for this study.[13]

RESULTS

Of 37 patients initially included, 32 completed the study (86%). The reason for drop-out was not related to adverse events or treatment failure, but to change of diagnosis (n = 2), withdrawal of agreement (n = 1) and loss to follow-up (n = 2).

In all, 15 patients were randomly assigned to the long-term treatment group and 17 patients to the short-term treatment group. Table 1 shows the characteristics of these patients. We found no statistically significant differences in the documented clinical or laboratory characteristics of the two treatment groups at the beginning of the study (table 2).

At the end of the trial, 2 of 13 patients (15%) with prolonged antibiotic therapy and 2 of 15 (13%) patients with short-term antibiotic treatment went into remission

Table 2 Baseline parameters of disease activity in 32 patients with *Chlamydia trachomatis*-reactive arthritis before receiving study drug

	Placebo group (n = 17) 10 days doxycycline*	Doxycycline group (n = 15) 4 months doxycycline*	p Value
Swollen joints	2.8 (1.5)	2.5 (2.5)	NS
Tender joints	3.8 (2.6)	2.3 (2.5)	NS
ESR (mm at the end of the first hour)	25 (17)	21 (16)	NS
CRP (mg/l)	2.9 (3.1)	1.5 (2.2)	NS
Pain intensity (0–10)	4.8 (2.1)	4.5 (1.8)	NS
Global assessment (0–10)	5.3 (2.2)	4.4 (1.5)	NS
Morning stiffness (min)	48 (45)	72 (85)	NS
Fatigue intensity (min)	188 (219)	144 (200)	NS
IgG titre to *Chlamydia* (x-fold)	5.6 (2.5)	5.6 (2.7)	NS
IgA titre to *Chlamydia* (x-fold)	1.5 (2.0)	2.0 (1.9)	NS

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; NS, not significant.
*Values are mean (SD).

Table 3 Disease outcome after 4 months in 32 patients with *Chlamydia trachomatis*-reactive arthritis receiving short-term or long-term treatment with doxycycline

	Placebo group (n = 17) 10 days doxycycline			Doxycycline group (n = 15) 4 months doxycycline			Comparison
	Entry	End	Mean (SD) change	Entry	End	Mean (SD) change	Mean difference (95% CI)
Swollen joints	2.8	0.8	−2.1 (1.7)*	2.5	1.9	−0.6 (1.7)	−1.5 (−2.8 to −0.2)
Tender joints	3.8	1.7	−2.2 (2.2)*	2.3	2.4	0.1 (1.8)	−2.3 (−3.8 to −0.8)
ESR (mm at the end of the first hour)	25	11	−14 (18)	21	14	−7 (14)	−7 (−19 to 5)
CRP (mg/l)	2.9	0.7	−2.1 (3.0)	1.5	0.9	−0.8 (2.3)	−1.4 (−3.5 to 0.7)
Pain intensity (VAS)	4.8	2.3	−2.5 (2.1)*	4.5	3.1	−1.1 (2.6)	−1.4 (−3.2 to 0.4)
Global assessment (VAS)	5.3	2.3	−3.1 (3.0)*	4.4	3.1	−1.2 (2.6)	−1.8 (−4.0 to 0.4)
Morning stiffness (min)	48	19	−33 (50)	72	48	−17 (73)	−16 (−64 to 32)
Fatigue intensity (min)	188	140	−61 (262)	144	81	−21 (45)	−40 (−192 to 111)
IgG titre to *Chlamydia* (x-fold)	5.6	4.9	−0.8 (1.9)	5.6	4.8	−0.9 (2.8)	−0.04 (−1.7 to 1.8)
IgA titre to *Chlamydia* (x-fold)	1.5	1.2	−0.4 (1.2)	2.0	1.0	−1.1 (1.8)	−0.8 (−0.3 to 1.9)

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; VAS, visual analogue scale (0, best; 10, worst).
*Significant.

(2 patients in each group could not be evaluated owing to missing values).

In the group with 4-month doxycyline treatment, although all clinical and laboratory parameters of disease activity except the number of tender joints decreased, none of the changes was significant. In contrast, in the short-term treatment group, all parameters improved and four of the improvements were significant: number of tender and number of swollen joints, intensity of pain, and patient's global assessment (table 3). When the two groups were compared, we found no significant difference regarding outcome for the different parameters examined (table 3).

DISCUSSION

To our knowledge, this study is the first prospective, randomised, double-blind, placebo-controlled trial on patients only with well-defined Ct-ReA, who are not taking concomitant drugs that are known to influence the activity and the course of the disease.

The predefined primary parameter for efficacy was similar in the prolonged doxycycline treatment group and the placebo group, thus showing no advantage of prolonged treatment with doxycycline for treatment of Ct-ReA.

Surprisingly, for the secondary end points of this trial, there was a tendency for reduced joint inflammation in the placebo group. Although this trend may be the result of chance, in vitro data suggest the induction of chlamydial persistence by long-term antibiotics,[14] and in vivo investigations describe persisting *C trachomatis* in joint tissue samples despite prolonged treatment with antibiotic.[15]

Disease duration and activity before treatment with antibiotic are probably relevant for the outcome. In the study of Lauhio *et al*[9] showing considerably better outcome for the prolonged antibiotic treatment group compared with the control group, patients had shorter disease duration (2.5 *v* 16.5 months), more active joint inflammation (ESR 48 *v* 23 mm at the end of the first hour) and were younger (28 *v* 42 years) than those in this study. Additionally, that study[9] included less patients (17 *v* 32) than our study, study entry occurred only after the initial 10-day treatment with antibiotics and treatment with intra-articular steroids, and sulfasalazine was permitted.

In vitro studies show an advantage of azithromycin over ciprofloxacin in the suppression of intracellular infection with *C trachomatis*; furthermore, a combination of azithromycin and rifampicin seems to be more effective than azithromycin alone to eliminate the organism.[16] Thus, further controlled studies with new treatment strategies including antibiotic combination therapy for patients with Ct-ReA are warranted.

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