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NO BENEFIT OF LONG-TERM CIPROFLOXACIN TREATMENT IN PATIENTS WITH REACTIVE ARTHRITIS AND UNDIFFERENTIATED OLIGOARTHRITIS

A Three-Month, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study

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Objective. **To investigate the effect of long-term antibiotic treatment in patients with reactive arthritis (ReA) and undifferentiated oligoarthritis.**

Methods. **One hundred twenty-six patients were treated with ciprofloxacin (500 mg twice a day) or placebo for 3 months, in a double-blind, randomized study. Of these patients, 104 (48 treated with ciprofloxacin and 56 treated with placebo) were valid for clinical evaluation: 55 were diagnosed as having ReA with a preceding symptomatic urogenic or enteric infection and 49 as having undifferentiated oligoarthritis. These 2 groups were randomized separately. The triggering bacterium was sought by serology and/or culture. The percentage of patients in remission after 3 months of treatment was chosen as the primary efficacy parameter.**

Results. **A triggering bacterium could be identified in 52 patients (50%): *Chlamydia trachomatis* in 13, *Yersinia* in 14, and *Salmonella* in 25. No patient was positive for *Campylobacter jejuni* or for *Shigella*. No difference in outcome was found between treatment with ciprofloxacin or placebo in the whole group or in subgroups of patients with ReA or undifferentiated oligoarthritis. No difference was seen in patients with a disease duration <3 months. Ciprofloxacin was not effective in *Yersinia*- or *Salmonella*-induced arthritis but seemed to be better than placebo in *Chlamydia*-induced arthritis. This difference was not significant, however, which might be due to the small sample size.**

Conclusion. **Long-term treatment of ReA with ciprofloxacin is not effective; however, it might be useful in the subgroup of patients who have *Chlamydia*-induced arthritis. This has to be proven in a bigger study focusing on patients with *Chlamydia*-induced arthritis.**

Reactive arthritis (ReA) occurs predominantly in young and middle-aged patients after an infection of the urogenital tract with *Chlamydia trachomatis* or an infection of the gut with *Yersinia*, *Salmonella*, *Shigella*, or *Campylobacter* (1). However, if the preceding infection is asymptomatic, such patients are mainly diagnosed as having undifferentiated oligoarthritis (2,3) because the identification of the triggering bacterium is normally difficult, especially if relying solely on serologic findings (4). Nonetheless, in some studies, ReA-associated bacteria were suspected to be triggering agents in ~30–40% of patients with undifferentiated oligoarthritis when more sophisticated techniques, such as antigen-specific T cell proliferation (3) or polymerase chain reaction (PCR) (5–7), were used.

ReA is often a self-limiting disease. Its mean disease duration has been reported to be between 3

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Table 1. Characteristics of patients with reactive arthritis and undifferentiated oligoarthritis treated with ciprofloxacin or placebo

	All patients (n = 104)		Patients with reactive arthritis (n = 55)		Patients with undifferentiated oligoarthritis (n = 49)	
	Ciprofloxacin	Placebo	Ciprofloxacin	Placebo	Ciprofloxacin	Placebo
No. of patients valid for evaluation at the end of treatment	49	55	27	28	22	27
Age, years						
Mean	37.2	36.7	37.3	35.5	37.1	38.0
Range	19–65	19–60	19–58	19–60	19–65	21–60
Sex, males/females	27/22	28/27	14/13	14/14	13/9	14/13
Disease duration, weeks						
Median	12	16	9	11	23	30
Range	1–354	1–260	1–208	1–260	2–354	4–210
% with disease duration <3 months	53.1	43.6	59.3	57.1	45.5	29.6
% HLA–B27 positive	39.6	41.8	53.8	50.0	31.8	33.3
No. of patients available at 6-month followup	39	49	20	25	19	24
No. of patients available at 12-month followup	39	48	19	24	19	24

months and 6 months. However, a substantial proportion of patients (~20%) experience a chronic course that continues longer than 12 months (8,9). Currently, patients are treated symptomatically with nonsteroidal antiinflammatory drugs (NSAIDs) or, in severe cases, with steroids, and those with chronic courses are treated with second-line drugs, such as sulfasalazine, which have been shown to be effective (10). To shorten self-limited courses and to treat chronic cases more effectively, a better and possibly curative treatment is needed.

The fact that ReA is triggered by a preceding bacterial infection and that bacteria or bacterial products can be detected in ReA patients' joints by various techniques (5–7,11–14) prompted several treatment trials with antibiotics (8,15). Indeed, in a clinically similar disease, Lyme arthritis due to persistence of *Borrelia burgdorferi* in the joint, the efficacy of antibiotic treatment has been convincingly demonstrated (16). However, the results reported so far for ReA have been less clear (17). Short-term antibiotic treatment of established ReA was clearly without any effect (18,19), while in small studies, treatment for >3 months showed some improvement in patients with *Chlamydia*-induced (8), but not those with enteric (8,15), ReA.

Herein we report the results of a 3-month, multicenter, double-blind, placebo-controlled study in which 104 patients with ReA or undifferentiated oligoarthritis were treated with ciprofloxacin, a quinolone with very good efficacy against enterobacteria and a moderate-to-good efficacy against *C trachomatis*. We found that long-term antibiotic treatment is not effective in any of these groups but that it might be of benefit in the subgroup of patients with *Chlamydia*-induced ReA.

PATIENTS AND METHODS

Patient selection and characteristics. In this study, 126 patients from 5 different rheumatology clinics in Berlin, Germany (Klinikum Benjamin Franklin, Rheumaklinik Buch, Rheumaklinik Wannsee, Charité, and Schlosspark Klinik), and from the Rheumatology Clinic Vogelsang, Germany, who had a diagnosis of ReA (n = 64) or undifferentiated oligoarthritis (n = 62) were included. Patients were stratified only for these 2 subgroups. A diagnosis of ReA was made if patients presented with a clinical picture of an asymmetric arthritis plus 1 of the following conditions: a preceding symptomatic urethritis or enteritis not longer than 4 weeks before the onset of arthritis, positive findings on examination of a urogenital swab for *C trachomatis*, positive findings on stool cultures for *Yersinia*, *Salmonella*, *Shigella*, or *Campylobacter*.

Other diagnoses were excluded by appropriate tests. A diagnosis of undifferentiated oligoarthritis was made after exclusion of other diagnoses if an asymmetrical oligoarthritis (<5 joints affected) was present and the criteria for ReA were not fulfilled. The patients' characteristics are shown in Tables 1 and 2.

Serology. In all patients, the following serologic tests (except the Widal) and immunoglobulin isotypes IgM, IgG, and IgA were investigated. Antibodies against *C trachomatis* were determined by using the microimmunofluorescence test (20): an IgG titer >1:64 plus the presence of IgA or IgM was regarded as positive. (Using these criteria, <0.7% of a local control population were antibody positive.) Anti–*Yersinia enterocolitica* and anti–*Yersinia pseudotuberculosis* antibodies were tested by enzyme-linked immunosorbent assay (ELISA) (21) and by agglutination test (Widal); anti–*Salmonella enteritidis* and anti–*Salmonella typhimurium* antibodies were tested

Table 2. Characteristics of patients with *Chlamydia*-induced arthritis and enteric reactive arthritis (*Yersinia* or *Salmonella* induced) treated with ciprofloxacin or placebo

	Patients with *Chlamydia* (n = 13)		Patients with *Yersinia* or *Salmonella* (n = 39)		Patients with *Yersinia* (n = 14)		Patients with *Salmonella* (n = 25)	
	Ciprofloxacin	Placebo	Ciprofloxacin	Placebo	Ciprofloxacin	Placebo	Ciprofloxacin	Placebo
No. of patients valid for evaluation at the end of treatment	8	5	14	25	5	9	9	16
% with disease duration <3 months	62.8	40	71.4	64.0	60.0	66.7	77.8	62.5
% HLA–B27 positive	50	20	57.1	64.0	60.0	66.7	55.6	62.5
No. of patients available at 6-month followup	6	5	11	20	4	7	7	13
No. of patients available at 12-month followup	6	4	10	20	4	7	6	13

by ELISA (22). *S enteritidis* and *S typhimurium* are estimated to be responsible for ~90% of cases of *Salmonella*-induced ReA, and most of the remaining *Salmonella* subtypes will probably also be recognized by the antibody test used (22,23). Anti–*Campylobacter jejuni* antibodies were also measured by ELISA. For this, the antigen was prepared from *C jejuni* using an acid glycine method as described by Kosunen et al (24). Antibodies against *Shigella flexneri* were not sought because a reliable test is not available. In the case of enterobacteria, antibody titers that were at least 2 standard deviations above the mean of a healthy control population from the Berlin area for at least IgG plus IgA or IgM were regarded as positive.

Bacteria in stool and urogenital cultures. Stool samples from each patient were examined for the presence of *Yersinia*, *Salmonella*, *Shigella*, and *C jejuni* using established cultural methods. For testing urogenital swabs for the presence of *C trachomatis*, *Chlamydia* were cultured on McCoy cell monolayers, and inclusion bodies were identified by immunofluorescence-labeled anti-*Chlamydia* antibodies (Kallestad/Pathfinder; Kallestad Diagnostics, Austin, TX).

Lymphocyte proliferation assay. A lymphocyte proliferation assay was performed on synovial fluid if available (22 ReA and 38 undifferentiated oligoarthritis patients), as previously described (3). The following heat-inactivated bacteria were used as antigens (final concentration 5 μg/ml each): *C trachomatis*, *Y enterocolitica* and *Y pseudotuberculosis*, *S enteritidis*, *S flexneri*, and *C jejuni*.

Identification of triggering bacterium. There are presently no generally accepted criteria for the identification of the triggering bacterium in ReA (4,25,26). The criteria shown in Table 3, always in the presence of an asymmetric arthritis, were used in this study to make a diagnosis of an arthritis that was probably or possibly induced by *C trachomatis* or by one of the enterobacteria.

Study design, administration of drugs, and concomitant medication. This study was a controlled, randomized, double-blind trial. Ciprofloxacin, 500 mg twice a day, or placebo was taken orally for 90 days. Patients with ReA and those with undifferentiated oligoarthritis were separately randomized for treatment with either ciprofloxacin or placebo. No medications other than NSAIDs were permitted throughout the study. Previous injections of glucocorticoids into joints and treatment with disease-modifying antirheumatic drugs (10 patients had previously been treated with sulfasalazine, 6 in the ciprofloxacin and 4 in the placebo group) were allowed until 4 weeks before the start of the study; no previous antibiotic treatment was permitted. Patients with positive findings on urogenital smears for *C trachomatis* (n = 11) or on stool cultures for enterobacteria (n = 2 for *S enteritidis*; n = 1 for *Y enterocolitica*) were first treated with 1,000 mg (two 500-mg capsules) of ciprofloxacin for 10 days. All patients were bacteria negative at the second evaluation.

Clinical and laboratory evaluation. Before treatment, a urogenital smear was evaluated for the presence of *C trachomatis*, a stool culture for the presence of enterobacteria, and antibodies against *C trachomatis* and enterobacteria were tested for as described above.

To evaluate response to treatment at months 0, 1, 2, 3, 6, and 12, the erythrocyte sedimentation rate and the C-reactive protein (CRP) level were determined and the following clinical data were obtained: an Articular Index score, patient's assessment of pain, patient's global assessment of health, physician's assessment of treatment success, and assessment for the presence/absence of remission. The clinical data were determined as follows.

The Articular Index score assessed each affected joint separately for tenderness to pressure (0 = not tender, 1 = tender, 2 = tender and the patient winced, 3 = tender and the patient winced and withdrew [27]), joint swelling (0 = not swollen, 1 = swollen, but swelling hardly visible, 2 = clearly swollen, joint shape still visible, 3 = swollen, joint shape no longer visible), and pain at rest (0 = no pain; 1 = pain). The resulting 3 values were summed to determine the Articular Index score. All joints were scored equally.

An Articular Index score was determined because in ReA and undifferentiated oligoarthritis, only 1 or a few joints (typically <5) are involved, and we wanted to quantify any improvement that occurred short of remission. Just counting the number of affected joints for tenderness and swelling would not have given us the same information in a mono- or oligoarticular disease. Unfortunately, unlike in a polyarticular arthritis such as rheumatoid arthritis, no evaluated activity score is available for ReA.

Patient's assessment of pain was made using a 10-point

Table 3. Criteria used to identify the triggering bacterium as a probable or possible cause of reactive arthritis or undifferentiated oligoarthritis

	Chlamydia	*Yersinia*	*Salmonella*	*Campylobacter*
Probable*	*Chlamydia*-positive urogenital smear *plus* symptomatic urethritis	*Yersinia*-positive stool culture	*Salmonella*-positive stool culture	*Campylobacter*-positive stool culture
	IgG ≥1:64 *plus* positive IgA or IgM† *plus* *Chlamydia*-positive urogenital smear *or* *Chlamydia*-specific lymphocyte proliferation†	Antibody titers 3 SD above normal† for IgG *plus* IgA or IgM	Antibody titers 3 SD above normal† for IgG *plus* IgA or IgM	Antibody titers 3 SD above normal† for IgG *plus* IgA or IgM
		Antibody titers 2 SD above normal† for IgG *plus* IgA or IgM *plus Yersinia*-specific synovial lymphocyte proliferation† *or* Widal agglutination >1:320 (normal <1:160)	Antibody titers 2 SD above normal† for IgG *plus* IgA or IgM *plus Salmonella*-specific synovial lymphocyte proliferation†	Antibody titers 2 SD above normal† for IgG *plus* IgA or IgM *plus Campylobacter*-specific synovial lymphocyte proliferation†
Possible	*Chlamydia*-positive urogenital smear *or* IgG ≥1:64 *plus* positive IgA or IgM†	Antibody titers 2 SD above normal† for IgG *plus* IgA or IgM *or* Widal agglutination >1:320 (normal <1:160)	Antibody titers 2 SD above normal† for IgG *plus* IgA or IgM	Antibody titers 2 SD above normal† for IgG *plus* IgA or IgM

* Only one criterion has to be fulfilled to be considered a probable cause.
† As defined in Patients and Methods.

visual analog scale (VAS), where 0 = no pain and 10 = most intense pain. Patient's global assessment of health was also made using a 10-point VAS, where 0 = very bad and 10 = very good. Physician's assessment of treatment success was graded as successful, partly successful, or no improvement. Remission was defined as no joint pain at rest, no swelling, mild tenderness (grade 1, as defined in the Articular Index score) at most, normal CRP level, and no relapse of arthritis (after remission) since the start of the study.

At months 1, 2, and 3, laboratory tests were done to detect side effects of treatment on the bone marrow (complete blood cell count including platelets), liver (gamma glutamyl transferase, serum glutamic oxaloacetic transaminase, alkaline phosphatase), and kidney (serum creatinine and urinalysis).

Statistical analysis. The percentage of patients whose disease was in remission at the end of treatment was chosen as the primary efficacy variable. The following secondary efficacy parameters were also used: the percentage of patients with a response to treatment (defined as a 50% decrease in the Articular Index score), patient's assessment of pain, patient's global health assessment, physician's assessment of treatment success (at the end of study only), and CRP level.

Analyses of the data for the followup visits were done separately. Additionally, changes between baseline and end of the trial and between baseline and followup visits 3 and 9 months after end of the trial were analyzed for the secondary efficacy parameters. The Cochran-Mantel-Haenszel test was used to assess the percentage of patients in remission and the percentage of patients with a 50% decrease in the Articular Index score. The other secondary efficacy variables were evaluated descriptively. Quantitative variables were analyzed in a 3-way analysis of covariance with pretreatment values as covariants.

Demographic and clinical data were analyzed descriptively. Treatment groups were compared with respect to age, body weight, sex, and the pretreatment parameters Articular Index score and CRP by analysis of covariance for the quantitative parameters and the Cochran-Mantel-Haenszel test for the variable of sex.

RESULTS

Subgroups of patients before start of treatment. The different subgroups of patients before the start of treatment are shown in Tables 1 and 2. Stratification was done only for the subgroups of ReA and undifferentiated oligoarthritis patients; therefore, in the other subgroups, the numbers of patients were not necessarily the same in the ciprofloxacin and placebo treatment groups. In 39 patients, *Yersinia* (n = 14; 8 with an initial diagnosis of ReA) or *Salmonella* (n = 25; 16 with an initial diagnosis of ReA) was identified as the probable (n = 9 for *Yersinia*, n = 15 for *Salmonella*) or possible triggering bacterium. *C trachomatis* was identified as the probable or possible cause of the arthritis in 13 patients. Ten of these patients had been classified as having ReA and 3 as having undifferentiated oligoarthritis at the beginning of the study. None of the 104 study patients (see next paragraph) had evidence of *C jejuni* or *S flexneri* or *Shigella sonnei* as the triggering microbe.

Patients valid for efficacy and followup evaluations. In the whole study group, 62 patients were included in the ciprofloxacin treatment group and 64 in

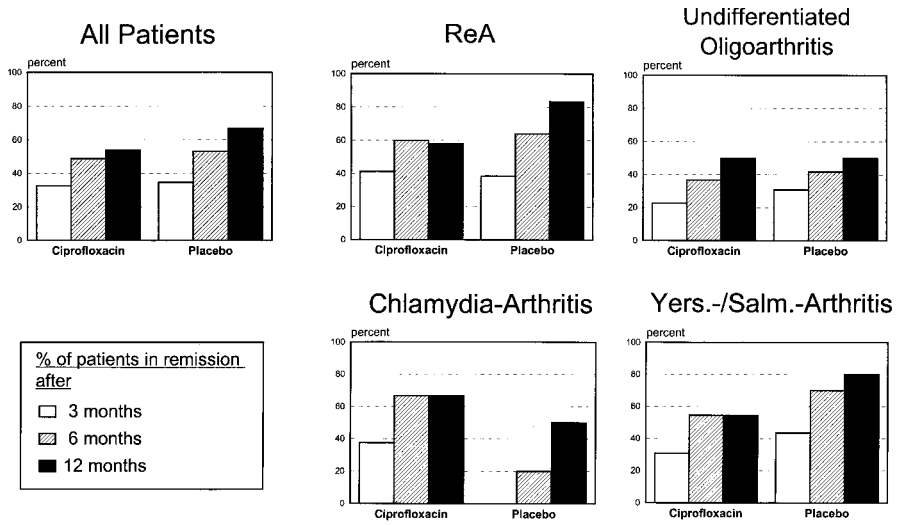

Figure 1. Percentage of patients in remission (as defined in Patients and Methods) among all patients and among subgroups of patients with reactive arthritis (ReA), undifferentiated oligoarthritis, *Chlamydia*-induced arthritis, and enteric arthritis (*Yersinia*-induced [Yers.] and *Salmonella*-induced [Salm.]) treated with ciprofloxacin or placebo after 3 months (end of treatment), 6 months (first followup), and 12 months (second followup). See Tables 1 and 2 for the numbers of patients available at followup.

the placebo treatment group. From these, 57 and 59 patients, respectively, were valid for intention to treat analyses, and 49 and 55, respectively, were valid for clinical evaluation (Tables 1 and 2). Only the results from the patients who were valid for clinical evaluation are presented. The reasons why patients were considered invalid for clinical evaluation were as follows: treatment <70 days (12 patients), lack of compliance (5 patients), and concurrent treatment with a drug that was not permitted (5 patients). The numbers of patients available for followup investigations at 6 and at 12 months after the start of treatment are shown for the various subgroups in Tables 1 and 2.

No effect of ciprofloxacin treatment in the whole study group or in the subgroups of patients with ReA or undifferentiated oligoarthritis. There was no significant difference in efficacy between the ciprofloxacin and the placebo groups at 3 months, 6 months, and 12 months after the start of treatment for the primary efficacy variable (percentage of patients in remission) (Figure 1), the secondary efficacy variables of improvement in the Articular Index score (Figure 2), percentage of patients with >50% improvement in the Articular Index score, or for any of the other secondary efficacy variables (results not shown). There was also no difference between patients treated with ciprofloxacin or placebo when patients with a disease duration of <3 months were analyzed separately (results not shown).

Interestingly, a considerable number of patients had symptoms for a long time, with the undifferentiated oligoarthritis patients doing slightly worse than the ReA patients. About one-third of all patients (35% ReA and 38% undifferentiated oligoarthritis) had an improvement of <50% after 6 months and 23.5% of all patients (24% ReA and 23% undifferentiated oligoarthritis) after 12 months. Furthermore, after 12 months of followup, 39% of the ReA patients and 50% of the undifferentiated oligoarthritis patients were still not in remission (Figure 1).

No effect of ciprofloxacin treatment on arthritis triggered by *Yersinia* or *Salmonella*. Fourteen of the patients with arthritis caused by enterobacteria were treated with ciprofloxacin and 25 with placebo. Age, sex, disease duration, and HLA–B27 positivity were similarly distributed among the 2 treatment groups (Table 2). Again, over the followup period of 12 months, no effect of ciprofloxacin was seen on the number of patients in remission (Figure 1), improvement in the Articular Index score (Figure 2), the number of patients with a 50% improvement, or on any of the other variables (results not shown). The results were similar when analyzed separately for these 2 bacteria and when ana-

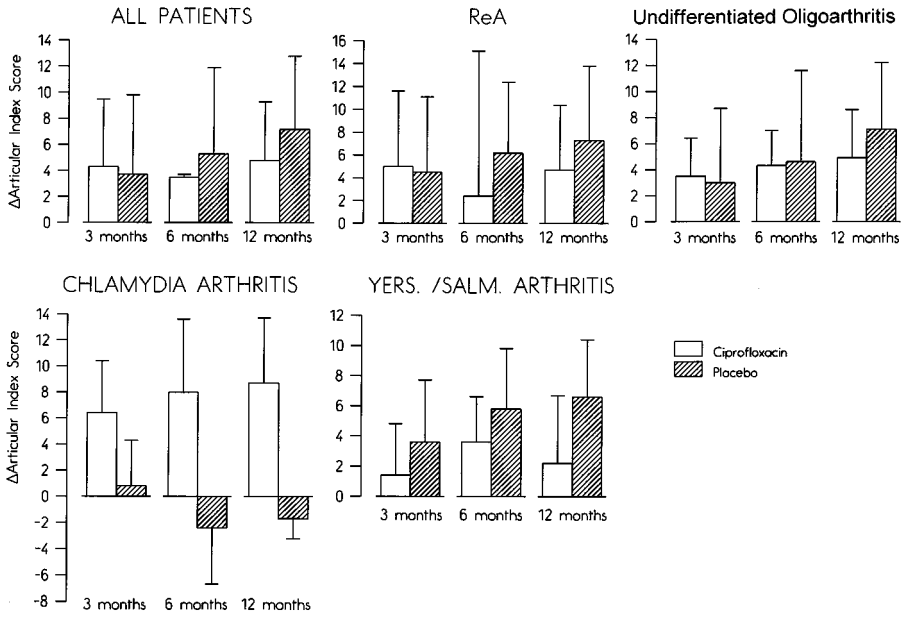

Figure 2. Improvement (difference [Δ]) in the Articular Index score (as defined in Patients and Methods) among all patients and among subgroups of patients with reactive arthritis (ReA), undifferentiated oligoarthritis, *Chlamydia*-induced arthritis, and enteric arthritis (*Yersinia*-induced [Yers.] and *Salmonella*-induced [Salm.]) treated with ciprofloxacin or placebo at different time points. Values are the mean and SD. See Tables 1 and 2 for the numbers of patients available at followup.

lyzed only for patients with probable *Yersinia*- or *Salmonella*-induced arthritis or only for patients with enterobacteria-induced arthritis with an initial diagnosis of ReA (results not shown). Most interestingly, for all variables, placebo was slightly better than ciprofloxacin (Figures 1 and 2).

Ciprofloxacin treatment in patients with *Chlamydia*-induced arthritis. In this group, all patients were included in whom *C trachomatis* could possibly or probably be identified as the triggering bacterium. In all the variables, except for patient's global health assessment (results not shown), a higher percentage of patients treated with ciprofloxacin showed an improvement compared with placebo (Figures 1 and 2). This difference was seen at each of the 3 followup visits and starting at the end of treatment. At the end of treatment, 37.5% of patients treated with ciprofloxacin, but none of those treated with placebo, were in remission (Figure 1). A similar difference was seen after 6 months (66.7% versus 20%), while this difference became smaller after 12 months (66.7% versus 50%). Furthermore, only in patients treated with ciprofloxacin could a clear improvement in the Articular Index score be observed, while even a deterioration could be observed in the placebo group at 6 and 12 months (Figure 2). At 6 months, 83.3% of the ciprofloxacin-treated patients had an improvement of >50% of their Articular Index score, compared with no patients in the placebo group. The shorter disease duration in the ciprofloxacin group could have meant a possible advantage, while the higher percentage of HLA–B27 positivity (Table 2) could have been a disadvantage for this group. However, due to the small number of patients with *Chlamydia*-induced ReA, none of the differences was significant.

No effect of ciprofloxacin treatment in any other subgroup. No effect or even a trend in favor of ciprofloxacin treatment was seen in any of the other subgroups shown in Tables 1 and 2 (results not shown).

Side effects of ciprofloxacin treatment. Surprisingly few side effects were observed during the 3-month period of ciprofloxacin treatment compared with placebo (Table 4). One patient in the ciprofloxacin group experienced a drop in the leukocyte count to 2.2/nl, which occurred 5 weeks after the start of treatment; there were no subjective symptoms in this patient, and a quick recovery occurred after cessation of treatment. Patients were withdrawn from the study (Table 4) for the following reasons: paraesthesia of the legs, dizziness,

Table 4. Number of patients with adverse drug effects in the ciprofloxacin and placebo treatment groups

	Ciprofloxacin		Placebo	
	No. with adverse effect	No. withdrawn because of adverse effect	No. with adverse effect	No. withdrawn because of adverse effect
Mild abdominal symptoms*	10	0	14	2
Mild neurologic symptoms†	8	1	5	0
Nonspecific symptoms‡	2	1	1	0
Granulocytopenia§	1	1	0	0
Other symptoms¶	7	1	5	1

* Diarrhea, constipation, abdominal pain, nausea, and vomiting.
† Headache, paraesthesia, depression, and sleeplessness.
‡ Fatigue and dizziness.
§ See Results for details.
¶ Heat sensations, pruritus, nocturnal palpitations, vaginal mycosis, dry mouth, and exanthema.

vaginal mycosis, and granulocytopenia in the ciprofloxacin group; diarrhea, nausea, and skin rash in the placebo group.

Power of the study. For the primary end point, remission after 3 months of treatment, the power for all patients was 86% for an assumed remission rate of 60% in the ciprofloxacin group versus 30% in the placebo group. The power for all patients was 57.6% for a remission rate of 50% versus 30%, respectively. For the small number of patients in the *Chlamydia* group, the power was <10%.

DISCUSSION

In the present study, we have shown that long-term ciprofloxacin treatment was not effective in the whole study group, in any of the stratified subgroups of patients with ReA or undifferentiated oligoarthritis, or in patients with enteric ReA. However, antibiotic treatment might work in *Chlamydia*-induced ReA.

ReA is generally regarded as a benign form of arthritis with a relatively high spontaneous recovery rate. In our study, 24% of ReA patients had improved <50%, and 39% were still not in remission after 12 months. These numbers are higher than those previously reported in patients with early ReA (8,9) and underline the importance of finding an effective treatment. In the present study, patients were diagnosed as having ReA in the presence of a preceding symptomatic infection or in the presence of bacteria in the stool or urogenital tract. We did not rely on serology for the initial diagnosis because there is no general agreement on the best serologic test for *C trachomatis*, and the specificity and sensitivity for the diagnosis of enteric ReA is often not clear for the commercially available tests (4,25,26). Thus, as the most important question in this study, we asked whether antibiotics are of any use in the treatment of ReA by applying diagnostic criteria that can be used in daily clinical practice. The results presented here show clearly that long-term antibiotics are not superior to placebo in patients with ReA if these criteria are applied.

We also studied a group of patients with undifferentiated oligoarthritis because a ReA-associated bacterium has been suggested to be the likely trigger in 30–40% of patients (3,5–7,14). Therefore, we reasoned that it would be of great importance for daily clinical practice if an effect could be shown in this group of patients without going through the present difficulties in identifying the causative bacterium. However, ciprofloxacin was also not effective in this group, a finding that is not surprising because of its failure in the ReA group.

We then raised the question whether this treatment was effective in subgroups in whom a causative microbe could be identified. We looked for bacteria in cultures of stool and urogenital swabs of all patients, and all the serologic tests were done at the end of the study, at the same time, and in experienced laboratories. The criteria we used to identify the triggering bacterium have not been validated, and therefore, their sensitivity and specificity are not known. Nonetheless, these criteria are similar or even stricter than those used in comparable studies (8,15,28). PCR for the detection of *C trachomatis* in the joint, which seems to be a promising diagnostic tool for the future, was not available at the start of the study.

Our study demonstrated that ciprofloxacin did not have an effect on the course of enteric ReA; this was

true for both *Yersinia*- and *Salmonella*-induced ReA. ReA due to a triggering infection with *C jejuni* or *Shigella* was not found. Although the numbers in these subgroups were relatively small, a treatment failure is likely because the placebo groups did slightly better than the ciprofloxacin group, making it unlikely that a larger number of study patients would have shown an effect in the latter group. It is also likely that other antibiotics are not more effective for enterobacteria because ciprofloxacin or other quinolones are currently the most effective drugs for the elimination of *Yersinia*, *Salmonella*, or *Shigella* (29). They also reach high concentrations in the joints and bones (30).

There are 2 previous placebo-controlled studies on the effect of a 3-month course of antibiotic treatment in ReA. However, no clear conclusions on the treatment of enteric ReA could be drawn from those studies. In the first study, Lauhio et al (8) treated 40 patients who had ReA with lymecycline or placebo for 3 months. No improvement was seen in the small subgroup of 11 patients with enteric ReA. Furthermore, lymecycline might have not been the most effective antibiotic for the elimination of enteric bacteria. In the second study, Toivanen et al (15) could not demonstrate an effect of ciprofloxacin treatment in 31 patients with *Yersinia*-induced ReA. The significance of this study was limited by the long disease duration of nearly 5 years before treatment.

The question arises as to why antibiotics fail in enteric ReA despite the detection of bacterial products (12–14,31) or even rarely of DNA (refs. 32 and 33 and Granfors K: unpublished observations for *Salmonella* DNA) in the joint. Most data on this question concern *Yersinia*. Despite considerable efforts (34), no DNA for *Yersinia* could be detected in joints in previous studies, suggesting that in most cases, no live bacteria are present. Only very recently has *Yersinia* DNA also been identified in the synovial fluid of 1 patient with ReA by use of a broad-spectrum PCR (33). In vitro studies showed that rod-shaped bacteria without DNA can be detected intracellularly for weeks by antibody staining (35). Thus, the persistence of dead bacteria could be sufficient for the stimulation of a local immune response over weeks and even over a few months, a duration often observed in the self-limiting form. The local inflammation could be caused, for example, by bacterial lipopolysaccharides, which are only slowly degraded. In this case, antibiotics would fail because no or only few live bacteria would be present.

Alternatively, antibiotics are ineffective despite persistence of live bacteria. Indeed, persistence of elevated IgA antibodies in patients with *Yersinia*-induced arthritis (36) and the results from animal models of *Yersinia*-induced arthritis (37) suggest that live *Yersinia* might persist in vivo outside the joint, most likely in the intestinal mucosa. In this case, the acute form of ReA might either run a course independently from extra-articular bacteria or antibiotics could fail to eliminate these bacteria for unknown reasons. In an animal model of *Yersinia*-induced arthritis, similar to ReA in humans, arthritis could not be prevented or improved when ciprofloxacin was given even at a very high dosage after the appearance of the first symptoms. Furthermore, ~15% of the animals continued to excrete *Yersinia* in the feces when treated with a dosage comparable with that used in humans (37). Taken together, current data indicate that acute and chronic forms of *Yersinia*-induced ReA cannot be influenced by currently available antibiotic treatment.

Fewer data are available for *Salmonella*-induced ReA or other enteric bacteria. Two studies showed that early antibiotic treatment of *Salmonella* enteritis, mostly with quinolones, did not prevent arthritis (38,39). Therefore, these studies plus our own findings suggest that antibiotics are also not effective in *Salmonella*-induced arthritis.

About 50% of all patients had a disease duration of <3 months. When this subgroup was analyzed, no effect of antibiotic treatment could be demonstrated, similar to the results found by Lauhio et al (8) for enteric ReA and similar to the experience in animal models (37).

The situation seems to be different in *Chlamydia*-induced arthritis. *C trachomatis* can persist in vivo in a latent form for years (5), and *Chlamydia* DNA (5–7) and even RNA (40) have been repeatedly found in the joints of ReA patients, indicating that live *Chlamydia* persist in the joint. Therefore, antibiotics could be more effective than in enteric ReA. Indeed, the data from our study and from the study by Lauhio et al (8) using 2 different antibiotics suggest that *Chlamydia*-induced arthritis can be successfully treated. In the latter study, a relatively small number of patients with *Chlamydia*-induced arthritis (n = 21) was treated with lymecycline or placebo. In the antibiotic-treated group, 50% of the patients recovered after 15 weeks, compared with 39.5 weeks in the placebo group, a statistically significant difference. In our present study, ciprofloxacin was also superior to placebo in nearly all variables at 3, 6, and 12 months after the start of treatment (Figures 1 and 2). However, due to the small number of patients with *Chlamydia*-

induced ReA, none of the differences reached significance.

While these studies suggest a beneficial effect of antibiotic treatment for *Chlamydia*-induced ReA, 2 other studies did not. In one of them, patients with *Chlamydia*-induced ReA who had a disease duration of >6 months were treated with 200 mg of doxycycline per day either for 2 weeks or 4 months (41), with no significant difference between the treatment groups. Furthermore, *C trachomatis* can persist in the synovial membrane despite treatment with adequate antibiotics, as has recently been demonstrated (42).

In contrast to gut infections with *Salmonella*, effective treatment of *C trachomatis* infection of the urogenital tract seems to prevent arthritis (43). Thus, the positive trend observed for antibiotic treatment in some of the studies including our own, the detection of chlamydial RNA in the joint indicating the persistence of live *Chlamydia*, and the prevention of arthritis by treating urogenital tract infections with antibiotics support a role for antibiotics in *Chlamydia*-induced arthritis. However, final proof is still missing, and a bigger study of only patients with *Chlamydia*-induced ReA, preferentially diagnosed by a *Chlamydia*-positive PCR result from a joint sample (5–7), is urgently needed. At the moment, it is not clear what the best antibiotic might be. In vitro studies and clinical experience suggest that tetracycline or macrolide antibiotics such as azithromycin are superior to the present quinolones for killing *Chlamydia*. To improve efficacy, even combination antibiotic therapy could be considered.

If antibiotics are only partly effective (*Chlamydia*-induced ReA) or not effective at all (enteric ReA) in the treatment of ReA, 2 other explanations have to be considered. First, bacteria might persist in a latent state, where they could be killed only by antibiotics in combination with stimulation of the immune response. We have indeed shown recently that patients with ReA have diminished secretion of tumor necrosis factor α (TNFα) after antigen-specific or mitogenic stimulation of mononuclear cells derived from synovial fluid (44) or peripheral blood (45); this can be reversed in vitro by stimulation with interleukin-12 (44). Thus, the relative lack of so-called T helper 1 cytokines such as interferon-γ and TNFα, which are necessary for fighting intracellular bacteria, might make patients susceptible to bacterial persistence and also partly resistant to antibiotics. Second, an autoimmune response might take over (46), especially in HLA–B27–positive patients, thus rendering antibiotic treatment ineffective. An immunosuppressive effect of ciprofloxacin has been described (47), but the treatment failure in the majority of patients compared with the effects of placebo makes it unlikely that this played any role in our study.

The 3-month treatment with ciprofloxacin had a surprisingly good safety profile, which was similar to that of placebo. The only serious side effect was the 1 patient who had a drop in the leukocyte count, with a prompt recovery after withdrawal of ciprofloxacin. Such an event has been reported to happen in <1% of patients treated with ciprofloxacin (48). The occurrence of musculoskeletal adverse effects in pediatric cystic fibrosis patients and an Achilles tendinopathy in renal transplant patients, both of whom were treated with ciprofloxacin, have been reported previously (49,50). However, we did not observe new musculoskeletal symptoms for which ciprofloxacin was considered a cause.

In summary, based on the results from our study, we cannot exclude that patients with very early enteric ReA would benefit if antibiotic treatment was started in the first days, although the lessons learned from animal models (37) and from studies of *Salmonella*-induced enteritis (38,39) argue against this possibility. In clinical practice, these patients are hardly ever seen by a physician that early, and are normally seen much later by a rheumatologist. Because the patients included in our study reflect the situation in daily clinical practice quite well, clinically relevant conclusions for antibiotic treatment of patients with ReA and suspected (possible) ReA can be drawn from our findings and those of the previous studies: 1) patients with ReA without the identification of the triggering bacterium and with *Yersinia*- or *Salmonella*-induced ReA should not be treated, 2) patients with possible ReA (undifferentiated oligoarthritis) should not be treated, 3) patients with *C trachomatis* in the urogenital tract should be treated short term, while the long-term treatment of *Chlamydia*-induced ReA is promising but has to be investigated further in larger studies focusing on patients with *C trachomatis* identified in the joint by PCR.

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