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CIPROFLOXACIN TREATMENT DOES NOT INFLUENCE COURSE OR RELAPSE RATE OF REACTIVE ARTHRITIS AND ANTERIOR UVEITIS

DENIS WAKEFIELD, PETER McCLUSKEY, MANJU VERMA, KARIM AZIZ, BARRIE GATUS, and GREGORY CARR

Objective. **To assess the efficacy of ciprofloxacin in the treatment of reactive arthritis (ReA) and anterior uveitis (AU) in a double-blind, randomized, placebo-controlled trial.**

Methods. **Seventy-two patients participated in this study, 56 with ReA and 42 with AU (26 patients had both ReA and AU). Ciprofloxacin (750 mg twice a day) was administered for 12 months with a 12-month followup. End points of the study included time to disease relapse and measures of disease severity.**

Results. **There was no difference between groups in time to disease relapse, joint inflammation, number of joints and enthesis involved in patients with ReA, or signs and symptoms of AU.**

Conclusion. **Long-term treatment of ReA and AU with ciprofloxacin made no statistically significant difference to the natural history of these diseases or their severity.**

Reactive arthritis (ReA) is an aseptic arthritis that often follows an inciting infection of the gastrointestinal or genitourinary tract. It may be complicated by the development of recurrent acute anterior uveitis (AU). A large variety of microorganisms have been implicated in the pathogenesis of ReA and AU (1,2). Although synovial fluid cultures are generally negative, several research groups have found bacterial antigens (3), bacteria-specific antibodies (4), and cytotoxic CD8+ T cells (5), as well as polymerase chain reaction evidence of microbial (chlamydial) nucleic acid (6,7) in the synovium and joint fluid of patients with ReA. Evidence supporting a role for pathogenic gut infection in ReA has also come from ileocolonoscopic studies that have shown acute inflammatory lesions on macroscopic and histologic examination (8). Further evidence for the role of infection in these diseases comes from the transgenic HLA–B27 rat model of disease, which has shown that HLA–B27 positive rats do not develop arthritis if they are kept in a germ-free environment (9).

Several studies have examined the role of antibiotics in ameliorating the natural course of ReA, but their findings have been inconclusive (10). We chose to assess the efficacy of ciprofloxacin in the treatment of ReA and AU because of its broad spectrum of activity against microorganisms implicated in the pathogenesis of these diseases, and because of its microbicidal activity, acceptable side effect profile, and tissue-penetrating ability.

PATIENTS AND METHODS

The study was a double-blind, randomized, placebo-controlled trial. Patients were randomly assigned to strata according to their HLA–B27 phenotype. The study was approved by the Prince of Wales Hospital Ethics Committee. After providing informed consent, patients were randomly assigned to receive either ciprofloxacin (750 mg twice a day) or placebo. The code for assignment of patients was not broken until the completion of the study. Both ciprofloxacin and placebo tablets were produced by Bayer AG (Sydney, Australia) and packed into numbered vials.

Patients were seen at regular intervals during this study—at enrollment, on ≥3 occasions during the 12 months of therapy, and on ≥3 occasions during the 12-month followup after stopping the drug. Laboratory assessment before commencing treatment included testing for the presence of HLA–B27 antigen, a complete blood cell count, liver function test, erythrocyte sedimentation rate, urinalysis, stool culture, rectal

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Denis Wakefield, MD, Peter McCluskey, MD, Manju Verma, MBBS, Karim Aziz, MD, Barrie Gatus, MD: University of New South Wales and Sutherland Centre of Immunology, South Eastern Area Health Services, Sydney, Australia; Gregory Carr, MBBS: Royal North Shore Hospital, Sydney, Australia.

Address reprint requests to Denis Wakefield, MD, Inflammation Research Unit, School of Pathology, University of New South Wales, Sydney, New South Wales 2052, Australia.

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swab and urethral or cervical swab, and serum levels of urea, electrolytes, and creatinine.

At each clinic visit, an ophthalmologist performed slit-lamp biomicroscopy and fundoscopy on patients with AU, and measured their visual acuity. Biomicroscopy was used to assess the anterior chamber (aqueous humor) flare, cells, and the presence of synechiae or other ocular complications, which were then noted for the purpose of deriving an examination score. This severity measure of AU was based on the grading system outlined by Hogan and colleagues (11). The symptom score was derived from the ophthalmologist's subjective assessment, based on the patients' symptoms (e.g., pain, photophobia, redness) and graded from 0 to 3 (maximum score 12). Patients with AU and ReA were admitted to the study if they met published criteria for these diseases (11,12).

The symptoms of patients with ReA were assessed by a physician at the baseline and each subsequent visit. A symptom score was calculated based on an assessment of the number of joints involved as well as on the following measures (graded from 0 to 3): amount of swelling, pain, and morning stiffness, and limitation of movement.

Statistical analysis. Separate analyses were performed for the ReA and AU disease groups. Data from patients who had both ReA and AU were included in each analysis. Time to first relapse was defined as the number of days between the baseline visit and the beginning of a disease relapse. The results were reported as life tables and Kaplan-Meier survival curves, and statistical significance was tested using the log rank statistic. The censoring point for these analyses was 1 year, that is, patients who remained in the study and did not relapse within 1 year of treatment were considered censored. Since a significant number of patients did not complete 1 year of treatment, those who neither relapsed nor completed 365 days of followup were treated in 2 ways by the analysis. They were considered censored at the time of last dose, or they were considered to have relapsed at the time of last dose. The analysis was performed on data from the following groups of patients: 1) the intent-to-treat population (all patients randomly assigned to treatment and receiving ≥1 dose of therapy), and 2) the efficacy population (those patients listed as compliant, where compliance was defined by physician assessment). A nonparametric test (Wilcoxon's 2-tailed test) was used to compare the changes in the 2 treatment groups.

RESULTS

Seventy-two patients participated in the study. The baseline characteristics of these patients are summarized in Table 1. Mean duration of disease before entering the trial varied from 4.6 months (range 1–24 months) for patients with ReA to 7.8 months (range 1–54 months) for patients with AU. Reasons for withdrawal included noncompliance (6 in ciprofloxacin group, 3 in placebo group), loss to followup (1 in ciprofloxacin group), and patient request to withdraw (6 in ciprofloxacin group, 8 in placebo group). Table 2 lists the reasons for patient withdrawals from the study, by treatment group. Thirteen of the 38 patients (34%) treated with ciprofloxacin and 14 of the 34 patients (41%) receiving placebo did not complete 1 year of treatment. Twenty-five patients in the ciprofloxacin group and 20 in the placebo group completed 1 year of treatment. The 95% confidence interval (95% CI) for the number of inflamed joints was −1.48 to 1.19, and the 95% CI for symptom score was −2.40 to 1.18.

Table 1. Summary of patient characteristics at baseline*

Characteristic	Ciprofloxacin group (n = 38)	Placebo group (n = 34)
Reactive arthritis only	16	14
Anterior uveitis only	9	7
Reactive arthritis and anterior uveitis	13	13
Total no. with reactive arthritis	29	27
Total no. with anterior uveitis	22	20
Women:men	9:29	11:23
HLA–B27 positive (%)	23 (61)	23 (68)
HLA–B27 negative (%)	15 (39)	11 (32)

* Values are the number of patients.

Time to first relapse. *ReA: intent-to-treat population*. The estimated failure rate (relapse rate) for the ReA patients at 1 year, when withdrawals were considered treatment failures, was 72% in the ciprofloxacin group and 62% in the placebo group (χ^2 = 0.75, 1 degree of freedom [df], P = 0.4). When withdrawals were considered censored, the corresponding rates were 49% for the ciprofloxacin group and 25% for the placebo group. The log rank did not achieve statistical significance (χ^2 = 2.8, 1 df, P = 0.9).

AU: intent-to-treat population. The estimated failure rate (relapse rate) for the patients with AU at 1 year, when withdrawals were considered treatment failures, was 73% in the ciprofloxacin group and 70% in the placebo group (χ^2 = 0.01, 1 df, P = 0.15). When withdrawals were considered censored, the corresponding rates were 64% for the ciprofloxacin group and 40% for the placebo group. The log rank did not achieve statistical significance (χ^2 = 2.2, 1 df, P = 0.14).

ReA: efficacy population. The estimated failure rate (relapse rate) for the ReA patients at 1 year, when withdrawals were considered treatment failures, was 71% in the ciprofloxacin group and 50% in the placebo group (χ^2 = 1.96, 1 df, P = 0.16). When withdrawals were considered censored, the corresponding rates were 56% for the ciprofloxacin group and 25% for the placebo group. The log rank did not achieve statistical significance (χ^2 = 2.94, 1 df, P = 0.09).

Table 2. Reasons for withdrawal*

Reason	Ciprofloxacin group (n = 38)	Placebo group (n = 34)
Adverse event	–	3
Noncompliance	6	3
Lost to followup	1	–
Patient request	6	8
Total no. of withdrawals	13	14
Completed 1 year of treatment	25	20

* Values are the number of patients.

AU: efficacy population. The estimated failure rate for the AU patients was 77% in the ciprofloxacin group and 50% in the placebo group ($\chi^2 = 2.05$, 1 df, $P = 0.09$). When withdrawals were considered censored, the corresponding rates were 77% for the ciprofloxacin group and 36% for the placebo group. There was a statistically significant difference between the ciprofloxacin and placebo groups ($\chi^2 = 3.89$, 1 df, $P = 0.05$).

Severity indices at baseline and 6 months. *ReA: intent-to-treat population.* Among the ReA patients, Wilcoxon's rank sum test for the comparison of the 2 treatment groups showed no statistically significant differences ($P = 0.98$ for number of joints, $P = 0.80$ for arthritis [joint] score) (Table 3). There was no relationship between duration of disease and response to treatment.

AU: intent-to-treat population. There was no indication of improvement in the severity of uveitis during this period for either treatment group ($P = 0.38$ for symptom score, $P = 0.65$ for examination score) (Table 4).

ReA: efficacy population. Among the ReA patients, there was a tendency toward improvement in both treatment groups. However, there was no significant difference between the 2 groups ($P = 0.94$ for number of joints, $P = 0.65$ for symptom score).

Table 3. Response to ciprofloxacin therapy by patients with reactive arthritis

	No. of patients	No. of joints (mean ± SD)*	Joint score (mean ± SD)†
Baseline			
Ciprofloxacin	29	3.13 ± 2.52	10.7 ± 11.9
Placebo	27	3.59 ± 3.09	11.26 ± 14.2
6 months			
Ciprofloxacin	27	2.04 ± 1.72	3.44 ± 3.34
Placebo	22	2.5 ± 2.4	5.32 ± 6.08
Change from baseline to 6 months			
Ciprofloxacin	27	−1.15 ± 2.85	−7.74 ± 12.95
Placebo	22	−1.18 ± 2.34	−6.68 ± 11.68

* $P = 0.98$, by Wilcoxon's rank sum test.
† $P = 0.80$, by Wilcoxon's rank sum test.

Table 4. Response to ciprofloxacin therapy by patients with anterior uveitis

	No. of patients	Symptom score (mean ± SD)*	Examination score (mean ± SD)†
Baseline			
Ciprofloxacin	22	1.73 ± 3.71	1.39 ± 2.34
Placebo	20	1.55 ± 2.06	1.7 ± 1.81
6 months			
Ciprofloxacin	22	1.91 ± 2.96	1.40 ± 2.27
Placebo	15	1.27 ± 1.94	1.93 ± 3.23
Change from baseline to 6 months			
Ciprofloxacin	22	0.18 ± 3.33	−0.05 ± 2.23
Placebo	15	−0.27 ± 2.71	0.5 ± 2.08

* $P = 0.38$, by Wilcoxon's rank sum test.
† $P = 0.65$, by Wilcoxon's rank sum test.

AU: efficacy population. There was no indication of improvement in the severity of uveitis during this period for either treatment group ($P = 0.54$ for symptom score, $P = 0.51$ for examination score).

Microbial cultures from 11 patients were positive at baseline (5 patients had >1 positive culture). Cultures from rectal swabs contained 1 *Salmonella* group E, 1 *Escherichia faecalis*, and 2 *Yersinia* species. Cultures from urethral swabs contained 3 *Chlamydia trachomatis* and 2 *Streptococcus* species group B. Cultures from conjunctival swabs contained 2 *C trachomatis* and 5 *Staphylococcus aureus.* Cultures from midstream urine contained 1 *E faecalis*.

At the time of disease relapse or at the completion of the trial, 5 patients had ≥1 positive microbial culture. Cultures from rectal swabs contained 1 *Yersinia* species (1 patient receiving placebo). Cultures from urethral swabs contained 3 *C trachomatis* (1 patient receiving placebo and 2 patients no longer receiving ciprofloxacin treatment), as well as 1 *Streptococcus* species (1 patient who received ciprofloxacin treatment). Cultures from conjunctival swabs contained 1 *C trachomatis* (1 patient no longer receiving ciprofloxacin treatment). Cultures from midstream urine contained 1 *Streptococcus* group B (1 patient no longer receiving ciprofloxacin treatment).

DISCUSSION

The results of this study indicate that the long-term treatment of patients with ReA and/or AU with ciprofloxacin made no significant difference to the se-

verity or natural history of these diseases. The natural history of ReA and AU is one of gradual improvement over time, and this was observed in both the ciprofloxacin and placebo groups in this study (12). We tested the effect of ciprofloxacin over a 12-month period, reasoning that earlier, shorter-duration studies had failed to show a response, and that this may have been due to the failure of short-term therapy to eradicate, or prevent reexposure to, the initiating microorganisms. Previous investigators had indicated that a longer duration of antibiotic therapy might have been necessary to assess the efficacy of this treatment approach (10). The findings of this study do not support such a contention.

Ciprofloxacin was well tolerated in large doses by patients in this trial over an extended period of time. This finding is similar to those obtained by Toivanen et al (13). In those authors' earlier study, prophylactic ciprofloxacin therapy was observed to have some beneficial effects in the treatment of chronic ReA. However, this was a short-duration study with a 6-month followup in which the treatment and control groups were not well matched, and in which only a few selected variables (arthralgia, pain on movement, and morning stiffness) had significant positive outcomes.

This is the first study to examine the role of antibiotics in preventing relapses of acute AU occurring either as an idiopathic disease or associated with ReA. Prophylactic treatment with ciprofloxacin showed no benefit in patients with recurrent AU.

There are several possible explanations for the failure of ciprofloxacin to alter the natural history of ReA and AU. It is possible that, in spite of appropriate antibiotic treatment, ReA- and AU-triggering microorganisms persist within the body in a nonviable or antigenic form (14). Microorganisms may initiate an immune response that subsequently becomes directed at self antigen and thus autoimmune, or microbes may be able to survive intracellularly in the presence of high antibiotic concentrations.

Further large, prospective studies with well-defined patient and control samples are needed to determine the role of antibiotics in the treatment of ReA and AU. Such studies should ideally involve patients with disease of recent onset triggered by a well-defined microorganism, and should include prolonged clinical and microbiologic monitoring.

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