EXTENDED REPORT

Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis

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Background: The value of antibiotics in the treatment of reactive arthritis (ReA) is still controversial.
Objectives: To analyse the long term outcome of patients with ReA, treated with a three month course of ciprofloxacin or placebo.
Methods: Patients who had had ReA and had participated in a double blind, placebo controlled trial on the effectiveness of ciprofloxacin 4–7 years earlier were invited to a clinical examination. Of the 71 patients who were included in the original study, 53 agreed to visit the clinic for an examination. Twenty six of 53 patients had originally received ciprofloxacin and 27 had belonged to the placebo group. Of these, 20 in the ciprofloxacin and 25 in the placebo group were HLA-B27 positive.
Results: 11/27 (41%) patients in the original placebo group had now developed chronic rheumatic disease, as compared with only 2/26 (8%) patients originally treated with ciprofloxacin (p=0.006). Two patients who originally had received placebo, none in the ciprofloxacin group had developed ankylosing spondylitis, and three patients in the original placebo group, none in the ciprofloxacin group had recurrent anterior uveitis. The same tendency was seen when several different measures were analysed. Of the patients with chronic spondyloarthropathy, 10 in the placebo and none in the ciprofloxacin group were HLA-B27 positive.
Conclusion: Analysis 4–7 years after the initial ReA suggests that a three month course of antibiotics in the acute phase may have a beneficial effect on the long term prognosis.

Reactive arthritis (ReA) is caused by an infection in genetically predisposed subjects. These infections affect in most instances mucosal membranes of either the gastrointestinal or urogenital tract. The list of known triggering microbes is long and includes among others salmonella, *Shigella flexneri*, *Campylobacter jejuni*, and yersinia causing enteric infections, and correspondingly *Chlamydia trachomatis* as a urogenital infection.[1 2]

The prognosis of ReA is generally considered to be good. However, this is not the case. Early studies by Paronen[3] and Sairanen *et al*[4] have shown that quite a proportion of the patients have chronic musculoskeletal symptoms even for several years. Recurrences may be triggered by new infections or non-specific stress factors.[5 6] Prolongation of ReA has proved to be rather common. Reports suggest a chronic course in from 4 to 19% of cases of yersinia, salmonella, shigella, or chlamydia triggered ReA.[7–9] Follow up studies suggest that 20–70% of patients have some joint pain, enthesopathy, or occasional attacks of low back pain for several years after ReA.[10–13] A few reports of fatal outcome due to severe amyloidosis complicating Reiter's disease have even been published.[10 14–17]

Immunological studies have suggested that the triggering microbe or components of it may persist in the patients, maintaining a prolonged immune response.[18] Indeed, bacterial antigens have been detected by immunofluorescence tests at the site of inflammation—for example, in the synovium and synovial fluid.[19–24] Assays involving molecular amplifications have been successfully used to demonstrate chlamydial DNA or RNA in joint specimens from patients with ReA.[25] Also, structures of yersinia have been shown to persist in the submucosa of the gut and in lymph nodes in patients with chronic yersinia triggered ReA.[26]

All this evidence has made attempts to eradicate the possibly persisting microbes a logical approach in the treatment of ReA.[27] Results for the impact of antimicrobial chemotherapy of enteric infections on the development of ReA have been contradictory. In three studies the effect of a short antibiotic course on ReA was very weak or absent. Joint symptoms could not be prevented by antibiotic treatment, nor did antibiotics affect the duration of ReA.[28–30] Recently, a study of the early use of antimicrobial chemotherapy indicated that fluoroquinolones had some effect in preventing the development of musculoskeletal symptoms following salmonellosis.[31] The early use of antimicrobial drugs probably does reduce the risk of postvenereal arthritis.[5] Some tendency to improvement has been seen with long term treatments lasting for months, not only in uroarthritis but also in enteroarthritis.[32–34]

Our group evaluated the effect of long term ciprofloxacin treatment on ReA in a prospective, randomised, placebo controlled trial.[35] Seventy one patients with acute ReA triggered by a gastrointestinal or urogenital infection were randomly assigned to receive ciprofloxacin 500 mg or placebo twice daily for three months. Thirty patients in the ciprofloxacin group had enteroarthritis (salmonella 11, yersinia 10, campylobacter 5, undefined 4) and 30 patients in the placebo group (salmonella 11, yersinia 10, campylobacter 7, *Clostridium difficile* 1, undefined 1). Uroarthritis was diagnosed in six patients in the ciprofloxacin group (chlamydia 2, *N gonorrhoeae* 1, undefined 3) and five patients in the placebo group (chlamydia 1, undefined 4). The patients were followed up for 12 months. There were no statistically significant differences in any of the primary or secondary efficacy parameters between the groups at baseline or during the 12 months' follow up. Further, no difference was seen when the enteroarthritis and uroarthritis

Abbreviations: AS, ankylosing spondylitis; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IBP, inflammatory back pain; IQR, interquartile range; ReA, reactive arthritis; SpA, spondyloarthropathy

groups were analysed separately. All primary outcome measures indicated that the condition of the patients as a whole group improved during the study.[35] A similar study was reported by Sieper *et al*,[36] with identical results. However, the effect of long term antimicrobial treatment on the late prognosis of ReA has not been studied. For this reason we have here evaluated the late prognosis in our patients who had received either ciprofloxacin or placebo for three months at the acute phase of the disease.

PATIENTS AND METHODS

Patients

In the original randomised, double blind, placebo controlled trial, between December 1992 and February 1996, 71 patients with acute ReA triggered by a gastrointestinal (60 patients) or urogenital (11 patients) infection were randomly assigned to receive ciprofloxacin 500 mg (36 patients) or placebo (35 patients) twice daily for three months.[35] Patients were primarily followed up for one year. In the present study the same patients were invited for a check-up visit to the clinic 4–7 years later. Fifty three patients were examined in the clinic, and 16 were interviewed by phone. Only the 53 patients who visited the clinic were included in the final analysis.

Methods

At the clinic visit patients were asked about their medical history after the acute ReA and after the end of the previous study. Special attention was given to possible signs of chronic spondyloarthropathy (SpA)—for example, relapses of arthritis, low back pain, episodes of anterior uveitis, inflammatory bowel disease (IBD), or rash. Complete recovery was defined as normal findings by the patients's global assessment, erythrocyte sedimentation (ESR), serum C reactive protein (CRP), white blood cell counts, and clinical examination.

Clinical evaluation

Clinical evaluation included general clinical and joint examination. The number of swollen joints, joint swelling score, and joint tenderness score (Ritchie index)[37] were calculated. Mobility impairment related to axial involvement was evaluated by the Schober test,[38] finger to floor distance, and chest expansion. The patient and the doctor assessed the overall disease activity on a 100 mm visual analogue scale (0= no activity, 100=maximum activity). Because the patient codes had been opened at the time of the analysis of the original study, it was impossible to "blind" the investigators.

Laboratory examinations

Laboratory examinations included general tests of blood and plasma: ESR, CRP, blood cell counts, alanine aminotransferase, alkaline phosphatase, creatinine, and urine analysis. All patients had been typed for HLA-B27 at the baseline of the previous trial. Levels of serum antibodies against the triggering microbes were determined individually for each patient according to the triggering infection. The methods are outlined in detail elsewhere.[35]

Radiographic evaluations

Radiographic evaluations were carried out for patients with suspected inflammatory back pain (IBP) or chronic symptoms in peripheral joints according to the investigator's consideration (affected peripheral joints, lumbar spine, sacroiliac joints). Magnetic resonance imaging was used in patients with suspected sacroiliitis. Abdominal scintigraphy with Tc labelled leucocytes was done in patients with active SpA (European Spondylarthropathy Study Group 1991 criteria).[39]

Statistical analysis

Data were analysed by the statistical package for the social sciences for Windows (release 9.0, SPSS; Norusis/SPSS, Inc, Chicago, IL, USA). For variables with a normal distribution descriptive values were expressed as means and standard deviations (SD) and statistical comparisons between measures of groups were made by Student's *t* test. If the variables were non-normally distributed descriptive values were expressed as medians and interquartile ranges (IQR), and statistical comparisons between groups were made with the Mann-Whitney U test. Measures with a discrete distribution were expressed as counts and percentages and were analysed by χ^2 test or Fisher's exact test. Statistical significance was set at the 5% level.

Table 1 Number of patients with chronic rheumatic disease at the end of the present study

	Ciprofloxacin group (n=26)	Placebo group (n=27)
Clinical findings		
AS	0	2
IBP	0	4†‡
Enthesitis	0	2
Chronic oligoarthritis	0	1‡
Psoriatic arthritis	1	0
Seronegative polyarthritis	1	0
Recurrent anterior uveitis	0	3†
Total	2*	11*
Diagnostic imaging		
Plain radiographs (n=11)		
Sacroiliitis and AS	0	2
OA of spine	1	1
MRI (n=6)		
Sacroiliitis	0	3
HLA-B27 positive		
All	20**	25**
Patients with chronic disease	0	10

*p=0.006; **non-significant difference (p=0.111); †one patient had both IBP and recurrent anterior uveitis; ‡one patient had both IBP and chronic oligoarthritis.
AS, ankylosing spondylitis; IBP, inflammatory back pain; OA, osteoarthritis; MRI, magnetic resonance imaging.

RESULTS

The present clinical follow up study included 53 (23 female, 30 male) of the 71 patients from the original study.[35] The group originally treated with ciprofloxacin at the acute phase comprised 26 patients with a mean age of 36 years (at the time of acute ReA), and the placebo group 27 patients with a mean age of 37 years. In the original study, 56 (79%) patients were HLA-B27 positive. In the present study HLA-B27 was positive in 45/53 (85%) patients attending a clinical visit and correspondingly 11/16 (69%) in the patients interviewed by phone. In the ciprofloxacin group 20/26 and in the placebo group 25/27 were HLA-B27 positive (table 1). A comparison was carried out to see whether the patients who now were clinically re-examined and those interviewed by phone were truly comparable. No significant differences between them could be found at the baseline of the original study (table 2). Two patients could not be reached even by phone.

Spinal symptoms

Pertinent medical histories included IBP in nine patients, two in the active, and seven in the placebo group. Two patients in the placebo group fulfilled the criteria for ankylosing spondylitis (AS)[40] and had radiological evidence of sacroiliitis. They also had other typical radiological features of AS. Both had vertebral squaring, and one also had syndesmophytes on the lumbar vertebrae. Six of the patients with suspected IBP were studied using magnetic resonance imaging of the sacroiliac joints. Sacroiliitis was detected in three patients in the placebo group, but in none in the active treatment group. Plain radiographs were taken from 11 patients (four active, seven placebo) because of IBP and clinical symptoms referring to

Table 2 Comparison of group characteristics at baseline of the original study. Values are shown as means (SD) unless stated otherwise

	Initial patients (n=71)	Clinic visit* (n=53, 75%)	Phone interview* (n=16, 23%)
Age (years)	36.2 (12.4)	36.8 (12.4)	34.5 (12.7)
Duration of disease (days)	42.4 (50.3)	34.9 (23.7)	43.9 (29.2)
Sex			
Female, No (%)	28 (39)	23 (43)	5 (31)
Male, No (%)	43 (61)	30 (57)	11 (69)
Number of swollen joints	3.4 (1.7)	3.6 (1.7)	2.8 (1.4)
Joint tenderness score	6.2 (2.9)	6.1 (2.8)	6.6 (3.2)
Joint swelling score	5.1 (2.7)	5.4 (2.7)	4.4 (2.4)
ESR (mm/1st h)	60.7 (26.8)	62.7 (27.1)	54.7 (25.7)
CRP (mg/l)	63.6 (50)	62.2 (45.2)	67.0 (62.6)
HLA-B27 positive†	56 (79)	45 (85)	11 (69)

*Two male patients in the placebo group were not available; †not determined in one patient.

sacroiliitis. In addition, one patient in each group had degenerative changes in the spine (table 3).

Sixteen patients were contacted by phone: one in the active group reported arthralgic pains in peripheral joints, one patient in the placebo group reported chronic low back pain, one patient in the active group had developed ulcerative colitis. However, he had been treated with ciprofloxacin only for a few days during the original study. The study drug had been discontinued owing to severe colitis, and IBD was diagnosed later.

Abdominal scintigraphy with Tc labelled leucocytes was performed in six patients with SpA (2 sacroiliitis, 1 chronic ReA, 1 seronegative polyarthritis, 1 chronic uveitis, 1 IBD and chronic uveitis). Four of them were HLA-B27 positive, two negative. None of these six patients had gastrointestinal symptoms, but two out of five patients in the placebo group had signs of a mild bowel inflammation. The only patient in the ciprofloxacin group (No 12) showed no signs of inflammation (table 3).

Clinical evaluations

One patient in the active treatment group and two patients in the placebo group had swollen joints. The patient's assessment of the overall disease activity on a 100 mm visual analogue scale was 9.6 (SD 11.5) mm in the active and 16.1 (SD 17.7) mm in the placebo group (p=0.170), respectively. Two patients in the active treatment group and 11 patients in the placebo group had developed a chronic rheumatic disease. Correspondingly, 24 (92%) patients in the active and 16 (59%) in the placebo group had recovered (p=0.006, table 4). Joint tenderness score (Ritchie index) was 0 (IQR 0–0) in the active treatment and 0 (IQR 0–2) in the placebo group (p=0.211). Two patients in the placebo group had chronic enthesitis at the insertion of the Achilles tendon. One patient in the placebo group had chronic oligoarthritis and one patient in the active treatment group had developed seronegative polyarthritis (table 1). Four patients in the placebo group, but none in the active group reported chronic arthralgia.

Laboratory examinations

Laboratory measurements were normal in most of the patients and showed no statistically significant differences between the groups. The ESR was slightly higher in the placebo group (9.8 *v* 8.0 mm/1st h), but the difference was not significant (p=0.42, table 4). Serum antibodies of IgM, IgA, and IgG class against the triggering microbes showed a decreasing trend except that *Y enterocolitica* O:3 antibodies remained unchanged or even increased when compared with the levels at baseline. Another striking feature was that in salmonella triggered ReA antibodies against salmonella were now mostly negative in both treatment groups. Overall, there was no difference in the antibody levels according to the treatment groups.

Table 3 Characteristics of the patients with chronic disease

Patient No	Treatment group	Sex	Age	HLA-B27 +/−	Triggering microbe	ESR BL	ESR PS	Imaging	Clinical diagnosis at the end	Antibodies present
1	P	M	25	+	Salmonella	60	2	MRI: bilateral sacroiliitis Sci: mild inflammation	IBP	No
2	P	M	25	+	UD	52	2	ND	Unilateral Achilles tendinitis	ND
3	P	M	30	+	Salmonella	58	12	MRI: bilateral sacroilitis Sci: normal	Chronic ReA IBP	IgM +/− IgG +/−
4	P	F	37	+	Salmonella	92	24	MRI: unilateral sacroiliitis	IBP	No
5	P	F	46	+	Salmonella	92	14	Sci: normal	Recurrent uveitis	No
6	P	F	36	–	Yersinia	104	22	Sci: normal	Chronic ReA	IgG +
7	P	M	34	+	Campylobacter	100	21	Rtg: bilateral sacroliitis, vertebral squaring, syndesmophytes	AS	IgM +/−
8	P	F	40	+	Campylobacter	23	16	Rtg: OA of lumbal spine MRI: SI joints normal Sci: mild inflammation	Recurrent uveitis IBP	IgM + IgA + IgG +
9	P	F	29	+	Salmonella	20	3	ND	Recurrent uveitis	No
10	P	M	30	+	Salmonella	46	13	Rtg: bilateral sacroiliitis, vertebral squaring	AS	No
11	P	M	51	+	Campylobacter	58	7	ND	Unilateral Achilles tendinitis	IgM +/−, IgA ++, IgG ++
12	C	F	65	–	Salmonella	18	4	Rtg: lumbar disc degeneration, SI joints normal Sci: normal	Seronegative polyarthritis	IgG +
13	C	M	44	–	Campylobacter	49	35	Rtg: SI joints normal	Psoriatic arthritis	IgG +/−

F, female; M, male; UD, undefined; ESR, erythrocyte sedimentation rate; BL, baseline of the original study; PS, present study; MRI, magnetic resonance imaging; Rtg, radiological finding; Sci, abdominal scintigraphic finding; ND, not done; SI, sacroiliac; OA, osteoarthrosis; IBP, inflammatory back pain; ReA, reactive arthritis; AS, ankylosing spondylitis

Table 4 Changes in four outcome variables by treatment group

	Baseline at the original study		At the end of the present study		
	Ciprofloxacin group (n=26)	Placebo group (n=27)	Ciprofloxacin group (n=26)	Placebo group (n=27)	p Value
ESR (mm/1st h)*	56.6 (27.1)	68.6 (26.2)	8.0 (7.7)	9.8 (8.5)	0.42
Patient's global assessment (VAS)*	33.3 (19.0)	29.8 (17.0)	9.6 (11.5)	16.1 (17.7)	0.170
Ritchie index	6.7 (3.3)*	5.9 (2.9)*	0 (0–0)†	0 (0–2)†	0.211
Complete recovery (%)‡	0	0	24 (92)	16 (59)	0.006

*Mean (SD); †median (IQR); ‡number of patients (%).
ESR, erythrocyte sedimentation rate; VAS, visual analogue scale. p Value refers to the difference between the ciprofloxacin and placebo groups at the present study.

DISCUSSION

In the present study, carried out 4–7 years after the initial ReA, it turned out that 11 patients in the placebo group and only two patients in the active treatment group had developed chronic articular disease. The result is surprising considering that in our previous study during a 12 month follow up after the acute phase of arthritis no statistically significant differences were seen in any of the primary or secondary efficacy variables between the ciprofloxacin and placebo treated groups.[35] Also, the study by Sieper *et al* showed identical results.[36] A most important result was that complete recovery was now significantly greater in the group who had received ciprofloxacin treatment.

The patients included in this study had had acute ReA at entry to the previous study, and a clear tendency towards recovery in both treatment groups was seen during the original 12 month follow up. Spondyloarthropathy includes in addition to ReA some other entities such as AS, PsA, IBD related arthritis, and undifferentiated SpA. Most of our patients were in permanent remission at the end of our original study, and the present result cannot be explained by an undulation of the disease.

Thirteen (25%) of the 53 patients attending a clinical evaluation at the present study had developed chronic rheumatic disease. However, none of the patients had developed a serious disability. A striking feature among the placebo treated patients with chronic disease course was that 10/11 were positive for HLA-B27. The two patients with chronic disease in the ciprofloxacin group were HLA-B27 negative. The correlation between HLA-B27 positivity and the development of more severe and prolonged course of ReA has been well established,[10 41] although chronic development may occur also in HLA-B27 negative subjects.[42]

In most patients the disease was caused by an enteric infection. The triggering microbe had been defined in 12/13 patients with chronic disease. Salmonella was the most common pathogen (7), followed by campylobacter (4), and yersinia (1). In this respect the material differs from that of many earlier studies, in which ReA triggered by urogenital infection was more common.[32 36 43] In these reports it has been suggested that in chlamydia triggered ReA antibiotics may be more effective than in enteroarthritis. The triggering microbe hardly plays any part in the present analysis.

Animal studies using a yersinia triggered model of ReA have yielded results which are in agreement with earlier clinical observations. Thus, the development of yersinia triggered ReA was prevented when a seven day course of ciprofloxacin was started early enough, before any signs of arthritis had appeared. However, if the treatment was started at the peak of the arthritis, no effect could be detected.[44] The same results were obtained when ciprofloxacin was given for a longer period of three weeks.[45] Antibiotic treatment favoured long term persistence of the microbe, with positive isolations from various organs and faeces. In other words, the disease could be prevented only when antibiotics were applied very early during the development phase of ReA.[27]

The present results raise a few questions. All available evidence so far suggests that when the immune reaction leading to ReA has started, elimination of the triggering microbe can no longer stop the process. Might, after all, prolonged antibiotic treatment have eradicated microbes that maintained or reactivated the ReA in those patients receiving placebo in the acute phase? The antibody profiles of the patients do not give any clue about this. The only definitely persisting antibody levels were in two patients who had had campylobacter as the triggering factor. The strong association of poor long term prognosis with HLA-B27 is another intriguing factor. At the start, the proportions of the study groups who had HLA-B27 were practically identical, and yet in the final analysis, 10/13 patients with chronic rheumatic disease, in contrast with none in the group with no symptoms, belonged to those positive for HLA-B27.

At present it is not possible to give a definite explanation for the results. Nevertheless, our results strongly suggest that antibiotic treatment may, after all, prevent the chronic consequences of ReA, especially in HLA-B27 positive subjects. The eradication of bacteria in the acute phase of ReA appears to be of great importance, especially in this subgroup.

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