EXTENDED REPORT

Antibiotic treatment and long term prognosis of reactive arthritis

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Objective: To evaluate whether a three month course of lymecycline has an effect on the long term prognosis of reactive arthritis (ReA).

Methods: In 1987-88 a double-blind controlled study with three month course of lymecycline/placebo was conducted. 17 of 23 patients treated at the outpatient department of Helsinki University Central Hospital volunteered to take part in a follow up study, where a physical examination were performed, and erythrocyte sedimentation rate, C reactive protein, rheumatoid factor, and radiographs of the lumbosacral spine and sacroiliac joints and of symptomatic peripheral joints were examined.

Results: 16/17 (94%) patients reported some kind of back pain and 10/17 (59%) peripheral joint symptoms during the follow up. Two patients had unilateral grade 1 sacroiliitis, one patient grade 4 sacroiliitis, and one patient bilateral grade 2 sacroiliitis. In one patient the disease had progressed to ankylosing spondylitis (AS), and in another to chronic spondyloarthropathy. In addition, two patients had small erosions in radiocarpal joints. No statistically significant differences were found between placebo and lymecycline groups in the development of chronic arthritis, sacroiliitis, or AS.

Conclusion: The results of the initial study showed that long term treatment with lymecycline in patients with acute ReA decreased the duration of arthritis in those with *Chlamydia trachomatis* triggered ReA, but not in other patients with ReA. Ten years after the acute arthritis one patient had developed AS, and three had radiological sacroiliitis, three patients had radiological changes at peripheral joints. Long term lymecycline treatment did not change the natural history of the disease.

Reactive arthritis (ReA) is an aseptic arthritis that follows infection of the gastrointestinal or genitourinary tract. Several classifications of ReA have been proposed during the past years,^{1,2} most recent classifications emphasising accurate diagnostic evaluation of the causing infection. The arthritis may also be complicated by extra-articular involvement, enthesitis, dactylitis, and the development of acute anterior uveitis or conjunctivitis. The human leucocyte antigen (HLA)-B27 is linked to ReA, 60-90% of patients with ReA being HLA-B27 positive. The pathogenetic mechanisms of ReA are still poorly understood and the treatment consists mainly of anti-inflammatory drugs or corticosteroids. Treatment of ReA with antimicrobial drugs has so far remained controversial. In a previous study we showed that duration of the illness in patients with *Chlamydia trachomatis* triggered ReA was shorter in those treated with lymecycline for three months than in a placebo treated group.³ Other studies of the long term treatment of acute ReA with ciprofloxacin showed no advantage over placebo treatment on the outcome of ReA.⁴⁻⁶

Prognosis in the majority of patients with acute ReA is usually good, with most patients gradually recovering in a few months. A recurrent attack of ReA is common in patients with chlamydia triggered arthritis.^{7,8} The long term prognosis may be not as good as earlier believed, for two thirds of patients have prolonged joint discomfort, low back pain, or enthesopathy symptoms after the acute ReA, and 15-30% of patients will develop chronic inflammatory disease of joints or back.⁷ Although the long term antibiotic treatment of acute ReA is not as promising as we first reported,³ we know very little about its effect on the long term prognosis of ReA. Therefore we set out to study the 10 year outcome of 17 patients with ReA treated for three months with lymecycline or placebo in the acute phase of ReA.

PATIENTS AND METHODS

We performed in 1987-88 a double blind, placebo controlled, randomised study of three months' lymecycline treatment in ReA triggered by chlamydia, yersinia, or campylobacter. The duration of the arthritis in patients with *Chlamydia trachomatis* triggered ReA was significantly shorter in those treated with lymecycline than in those given placebo, but not in patients with other forms of ReA.³ The primary study comprised 40 patients with the following baseline characteristics: (a) lymecycline group 21 patients (13 men, 8 women), mean (SD) age 30.9 (2.0) years; (b) placebo group 19 patients (15 men, 4 women), age 30.7 (1.9) years. The patients had the typical clinical picture of ReA. The preceding infection was verified by (a) *Chlamydia trachomatis* infection by isolation or by antigen detection, and/or by serology using the microimmunofluorescence test; (b) yersinia infection by stool culture or serology; (c) campylobacter infection verified by stool culture or serology; or (d) preceding urethritis or gastroenteritis, but with no isolation of, or serological evidence of, the triggering microbe. Only patients without previous antimicrobial treatment of the current episode of ReA were included in the study. Patients received lymecycline (300 mg three times a day) or identical placebo for three months. No concomitant drugs other than non-steroidal anti-inflammatory drugs or intra-articular corticosteroids were permitted. For chronically ill patients who failed to show any response to the treatment and had joint swelling for more than six months, sulfasalazine (SSZ) (1000 g twice a day) was started. Patients also received physical therapy.

Of the 40 patients in the primary study, we invited by letter 23 patients originally treated at the outpatient department of

Abbreviations: AS, ankylosing spondylitis; LS, lumbosacral; ReA, reactive arthritis; SI, sacroiliac; SSZ, sulfasalazine

Table 1 Characteristics of the patients during the index attack

	Lymecycline group (n=9)	Placebo group (n=8)	Total (n=17)
Age			
Mean (range)	36.1 (19–52)	32 (16–42)	34.2 (16–52)
Female	39.6 (19–52)	39	39.5 (19–52)
Male	31.8 (23–40)	31 (16–42)	31.3 (16–42)
Sex			
Female	5 (56%)	1 (13%)	6 (35%)
Male	4 (44%)	7 (87%)	11 (65%)
Triggering microbe			
Chlamydia	1	2	3
Yersinia	3	2	5
Campylobacter	1	1	2
Preceding urethritis	0	2	2
Preceding enteritis	3	1	4
No symptoms	1	0	1
Low back pain	4 (44%)	5 (63%)	9 (53%)
Number of tender joints			
Median (range)	3 (2–5)	3 (0–6)	3 (0–6)
Number of swollen joints			
Median (range)	4 (1–5)	2 (0–5)	2.5 (0–5)

the Helsinki University Central Hospital to the follow up study during the summer 1998. Patients who did not reply after the first letter were sent a second one. Four of the 23 patients did not respond to our request to participate. Of those 19 patients who replied, two were not willing to take part in the study, leaving 17 patients available for assessment in the follow up study. The appropriate institutional ethics committee approved the study. Informed written consent was obtained from all patients participating in this study. Of those two who replied but were not willing to take part in the study, one reported having joint discomfort, and the other had been asymptomatic. Human leucocyte antigen (HLA)-B27 was positive in all patients. Among the patients included in the follow up, three patients had a duration of ReA >6 months and treatment with SSZ had been started.

The follow up study included a physical examination of each patient with relevant laboratory tests and radiological examination. Special attention was paid to the medical history during the past 10 years. The medical history included questions about lumbar pain, peripheral articular involvement (arthritis, dactylitis), enthesopathy (heel pain), and extra-articular disease (eye, skin, gut, urogenital symptoms). The patient was asked whether a sign or symptom had ever occurred during the follow up time, or was present during the follow up visit. The nature of the lumbar pain was also defined—occurrence during the night or early morning, association with morning stiffness, improvement/aggravation with exercise, or under mechanical strain. The laboratory values of erythrocyte sedimentation rate, C reactive protein level, and rheumatoid factor titre (by immunoturbidometry) were determined. An electrocardiogram was examined in 14 patients. Conventional plain radiography of the sacroiliac (SI) joints and lumbosacral (LS) spine was performed and radiographs evaluated for the presence of syndesmophytes or vertebral squaring. Radiographs of the LS spine and SI joints were obtained for all patients, and analysed by an experienced radiologist (LL) who was not aware of the clinical symptoms or the HLA status of the patients. Grading of the films was performed with the modified New York criteria according to van der Linden *et al.*⁹ When peripheral joint swelling and/or arthralgia occurred during the follow up, radiographs of the affected joints were also obtained.

Data were analysed by the NCSS statistical system. Data of the two treatment groups were compared by χ^2 test with Fisher's exact test, Student's *t* test, and the Mann-Whitney test.

RESULTS

The follow up study was carried out a mean of 10.4 (range 8.2–11.5) years after the index attack of ReA. No significant difference in the mean follow up time of the treatment groups (lymecycline 10.3 and placebo 10.5 years) was found. Of the 17 patients taking part in the follow up study, 9 had received originally lymecycline and 8 placebo. Table 1 presents the baseline characteristics of the patients during the index attack. There were no statistically significant differences in the baseline characteristics between the treatment groups.

Table 2 presents the clinical and laboratory findings of the patients at follow up. Joint symptoms were mostly arthralgia or due to overexertion of single joint. There were no statistically significant differences between the treatment groups. One patient in each treatment group had positive rheumatoid factor. There were no marked limitations of LS spine mobility, Schober's test, or chest expansion measurements (data not shown). Instead, some patients had slightly restricted spinal mobility. The mean (range) distance of fingertips to floor was 5.1 cm (range 0–24). In six patients the distance was ≥ 5 cm; of these, two patients had degenerative changes of the LS spine, one had grade 4 sacroiliitis, and three did not have any radiological changes of the back.

Radiological findings were more consistent with degenerative than inflammatory disease (table 2). Bilateral grade 2 sacroiliitis was detected in one asymptomatic patient. Unilateral sacroiliitis was detected in three patients, two with grade 1 (one had also diffuse idiopathic skeletal hyperostosis), and one with grade 4 with the diagnosis of ankylosing spondylitis (AS). A total of six patients had single or multiple non-inflammatory findings in LS radiographs: scoliosis (three patients), degenerative changes in intervertebral discs (three patients), facet joint degeneration (one patient), and/or osteoarthritis of SI joints (one patient). The radiographs of the hands were examined in 9/17 (53%) patients, with small erosions found in the radiocarpal joints in two of the patients. The radiographs of the feet were examined in 9/17 (53%) patients; one of the patients had enthesopathic sporn in a toe, another had osteoarthritis. Radiographs of one or both knees were performed in six patients, with changes of osteoarthritis in one of the patients. One patient had enthesopathic changes in the ankle at radiography. An electrocardiogram was examined for 14/17 patients (82%). One patient had right branch bundle block, one early repolarisation changes, and one sinus arrhythmia. In conclusion three patients in the lymecycline group had radiological sacroiliitis (one patient grade 2 and

Table 2 Characteristics of the patients at the follow up visit

	Lymecycline group (n=9)	Placebo group (n=8)	Total (n=17)
Age			
Mean (range)	46.3 (30–63)	42.4 (26–52)	44.5 (26–63)
Female	49.6 (30–63)	50	49.7 (30–63)
Male	42.3 (33–51)	42.3 (26–52)	41.6 (26–52)
During follow up			
Low back pain	8 (89%)	8 (100%)	16 (94%)
Joint symptoms	4 (44%)	6 (75%)	10 (59%)
At follow up visit			
Low back pain	4 (44%)	3 (38%)	7 (42%)
Number of patients with tender joints	3 (33%)	3 (38%)	6 (35%)
Number of tender joints median (range)	0 (0–3)	0 (0–5)	0 (0–5)
Number of patients with swollen joints	1 (11%)	2 (25%)	3 (18%)
Number of swollen joints median (range)	0 (0–1)	0 (0–2)	0 (0–2)
Recurrent reactive arthritis	2	0	2
Recurrent iritis during follow up	1	2	3
Lumbosacral radiology			
Inflammatory lesions*	3	1	4
Non-inflammatory changes*	4	2	6

*Number of patients.

two patients grade 1), while three patients in the placebo group had radiological evidence of spondyloarthropathy (one AS, two enthesopathic changes in the peripheral joints).

The index attack was the first episode of ReA for 11 (65%) patients, the second for 5 (29%) patients, and the third for one (6%) patient. During the follow up two patients had had one recurrence each, the third attack in both of the patients. Three patients had had recurrent anterior acute uveitis; other extra-articular symptoms had not occurred during the follow up. Three patients with a prolonged index attack of ReA had been treated with SSZ for 1–8 months. Owing to persisting joint symptoms in one of them, treatment was later changed to auranofin. All the three patients slowly recovered from peripheral arthritis. One of the three patients remained asymptomatic during the follow up despite the bilateral grade 2 sacroiliitis. Another had low back pain with degenerative changes at radiography and arthralgia with the diagnosis of fibromyalgia, but no clinically or radiologically significant inflammatory findings. The third patient developed chronic spondyloarthropathy with arthralgia and synovitis and enthesopathic changes of ankle and toe at radiography.

DISCUSSION

During 10 years after acute ReA, musculoskeletal symptoms were common: 16/17 (94%) patients had had low back pain and 10/17 (59%) peripheral joint symptoms. Most patients did not have inflammatory rheumatic diseases at follow up; two (12%) patients had developed chronic rheumatic disease (one AS, another chronic spondyloarthropathy). Inflammatory radiological changes were detected in seven patients. The treatment strategy at the acute index attack had no major effect on the outcome of the patients. To the best of our knowledge, there are no previous studies on the effect of antimicrobial drugs on the long term prognosis of patients with ReA. Owing to the small number of patients in the study, no definite conclusions about the possible effect of antimicrobial treatment on the long term prognosis of ReA can be made. Our findings match those of earlier follow up studies of conventionally treated patients with acute ReA.^{7–10} Low back pain is often seen in patients without radiological sacroiliitis. Evidently, even HLA-B27 positive patients can have non-inflammatory back pain and degenerative spine changes.

It is clear that bacteria persist in patients with ReA. Bacterial degradation products and even DNA of several microorganisms have been detected in joint fluid/tissue from

patients with ReA.¹¹ The role of such disseminated microbial elements in the provocation or maintenance of arthritis remains unclear. Eradication of the causative microbe appears logical. In fact, we have shown previously that in patients with ReA triggered by *Chlamydia trachomatis*, the duration of arthritis was shorter in those receiving lymecycline than in those in the placebo group.³ The role of antibiotic treatment in ameliorating the natural course of ReA has been explored in several later studies, but solid evidence in favour of antibiotic treatment is still lacking.^{4–6} The eradication of microbes triggering ReA can be problematic. This is especially true for *Chlamydia trachomatis*, which has been shown to persist in the joint tissue in culture negative patients with Reiter's syndrome.¹²

Experimental and clinical studies have demonstrated that early antimicrobial treatment of a triggering infection before the development of arthritis is effective and can prevent ReA. Antibiotic treatment has been studied in an experimental model of yersinia triggered reactive arthritis in Lewis rats.¹³ The development of ReA was completely prevented if a three week course of ciprofloxacin was started early after infection, but not if the treatment was started at the time of well developed arthritis. Zhang *et al* showed that ciprofloxacin treatment resulted in increased faecal excretion of yersinia in rats.¹³ Antibiotic treatment might then even favour bacterial persistence. Bardin and his coworkers showed in a study in an Inuit Eskimo society that proper and prompt treatment of new genitourinary tract infections dramatically reduced relapses of ReA.¹⁴ Interestingly, we recently reported that early use of antimicrobial drugs might also prevent the development of musculoskeletal symptoms after human salmonella infection.¹⁵

Why has the antibiotic treatment failed to change the natural course of acute ReA? Our previous study showed no advantage of lymecycline treatment for the long term prognosis of ReA despite the effects shown in the index attack.³ Both the patients who developed chronic inflammatory rheumatic diseases were in the placebo treatment group (one with yersinia enteritis, another with *Chlamydia trachomatis* urethritis). Understanding how the bacteria infect the host might provide a different perception of the pathogenesis of arthritis. HLA-B27 has been found to be a predisposing genetic feature for development of arthritis. Interestingly, all our patients had HLA-B27. It has been considered that HLA-B27 present antigenic peptides to cytotoxic lymphocytes and in this way play a part in the development of arthritis. Other mechanisms and

molecular mimicry between HLA-B27 and bacterial molecules have also been considered. Several recent reviews emphasise the importance of the local immunological response in the joints and the possible role of T cell mediated autoimmune processes.^{11–16} The antimicrobial treatment has failed so far in the treatment of full-blown ReA and according to the present study does not influence the long term outcome. Because the number of patients we examined was relatively small, we are waiting to see more studies about the long term prognosis of patients with ReA treated with antimicrobial drugs.

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