

# Absence of radiographic progression of hip arthritis during infliximab treatment for ankylosing spondylitis

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**Abstract** This study aims to examine the impact of long-term treatment with the anti-TNF antibody infliximab on radiographic progression of hip arthritis in ankylosing spondylitis. Anteroposterior X-rays of the pelvis obtained at baseline from consecutive patients with ankylosing spondylitis and bilateral hip arthritis were compared with X-rays obtained after  $6 \pm 2.5$  years (mean  $\pm$  SD) of continuous infliximab treatment. Analysis was performed by the Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-h) scoring system (min 0, max 4). Hip joint space width was also assessed by the average of measurements at three distinct sites between the acetabulum and femoral head. In 23 patients with active disease (21 men, mean age and disease duration of 45 and 16 years, respectively), the BASRI-h score at baseline was 1 in 7, 2 in 16, 3 in 16, and 4 in 7 hips (including two arthroplasties). Individual BASRI-h scores at baseline ( $2.50 \pm 0.86$ , mean  $\pm$  SD) remained unchanged in all patients at end of follow-up. At baseline, the average width of the whole joint space ( $3.56 \pm 0.70$  mm,  $n=44$ ) was not associated with disease activity measurements but negatively correlated with BAS functional index (Spearman  $r=-0.5$ ,  $P=0.007$ ). After 2–10 years of infliximab treatment, the average width of the whole joint space in these patients ( $3.59 \pm 0.79$  mm) was not reduced. These results suggest that radiographic progression of hip

arthritis in ankylosing spondylitis may be arrested during infliximab treatment.

**Keywords** Ankylosing spondylitis · Hip · Infliximab · Radiographic progression

## Introduction

Hip involvement is the most frequent extraspinal arthritic manifestation of ankylosing spondylitis (AS) and a common cause of disability. According to data derived from three large datasets (ASPECT-REGISPONSER-RESPONDIA working group), clinical hip involvement is present in 24 to 36 % of AS patients, needing total replacement surgery in 5 % of them [1]. In addition to older age, higher Bath Ankylosing Disease Activity Index (BASDAI), and spinal changes, hip involvement contributes significantly to functional impairment, assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI). Moreover, a significant interaction between symptom duration and hip involvement has been described, indicating that patients with hip involvement were more likely to have severe spinal changes [2].

In contrast to the classical structural changes in the spine, hip joint inflammation in AS does not lead to formation of new bone but results in bone erosions and subsequent joint destruction [3], suggesting that during disease course both osteoproliferative and osteodestructive changes may occur in parallel at different sites. Whether radiographic progression in the spine is inhibited in patients receiving anti-TNF treatment when compared to historical controls remains elusive [4, 5]. On the other hand, whether anti-TNF treatment affects the progression of hip joint space narrowing in the long term in AS patients with preexisting hip arthritis is not known. To test the hypothesis that anti-TNF treatment interferes with osteodestructive changes in AS, as may happen in patients with rheumatoid arthritis [6], we retrospectively examined the

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impact of continuous long-term treatment with infliximab on radiographic progression of hip arthritis in AS.

## Patients and methods

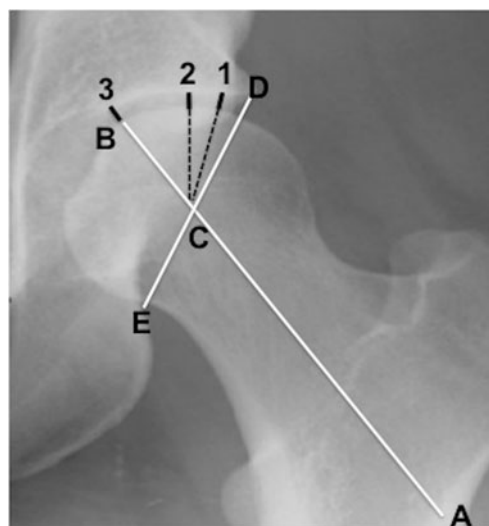
### Patients

In this retrospective study, all patients (21 men, 2 women) with hip involvement, derived from a total of 67 patients followed up in our rheumatology departments, who met the modified New York Criteria for definitive AS [7] and started infliximab treatment for active disease [8] not responding to NSAIDs between 2000 and 2008 participated. Hip involvement at baseline had been diagnosed by clinical signs and symptoms, such as pain and reduced range of motion. The clinical diagnosis had been confirmed radiographically as joint space narrowing and as having at least the score of 1 in Bath AS Radiology Hip Index (BASRI-h) scoring system (min 0, max 4). Two of 23 patients had undergone unilateral total hip replacement prior to initiation of infliximab treatment.

Anteroposterior X-rays of the pelvis were obtained after  $6.0 \pm 2.5$  years (mean  $\pm$  SD) of continuous treatment with infliximab from all 23 patients and compared with the respective baseline X-rays. In addition, individual BASFI, BASDAI, and CRP values at the end of follow-up were compared to the respective baseline measurements. The Veterans Administration Hospital Ethic Committee approved the study protocol.

### X-ray assessment

Both hips were scored separately using two different methods. Firstly, we used the BASRI-h scoring system, a reliable, disease-specific, sensitive to change method for grading hip radiographic change in AS with five severity grades, as follows: 0 = no change; 1 = possible focal joint space narrowing; 2 = definite narrowing, leaving a circumferential joint space  $>2$  mm; 3 = narrowing but with circumferential joint space  $\leq 2$  mm or bone-on-bone apposition  $<2$  cm; 4 = bone deformity or bone-on-bone apposition  $>2$  cm or total hip replacement [9]. Secondly, we used published methods [10, 11], previously applied for the estimation of the joint space width in patients with hip osteoarthritis, with slight modifications (Fig. 1). More specifically, joint space width was assessed by the average of measurements of interbone distance between the acetabulum and femoral head with the help of 0.1-mm graduated magnifying eyepiece at the following three distinct sites: (a) at 2 mm inner of the external end of the acetabulum after excluding any osteophytes, (b) on the vertical line through the femoral head center, and (c) on the head–neck center line, right before the widening formed by the capital fossa.



**Fig. 1** Three distinct sites of interbone distance in anteroposterior X-rays of the pelvis: 1, 2 mm inner of the external end of the acetabulum; 2, vertical line through femoral head center; 3, head–neck center line. C, center of the femoral head. AB, head–neck center line; DE, line connecting the outer edge of acetabulum and the inner edge of the femoral head where head loses sphericity

The center of the femoral head was determined by the intersection of the head–neck center line and the line that connects the outer edge of the acetabulum (excluding any osteophytes) and the inner edge of the femoral head, where the head loses sphericity. For each patient, the mean space width of the left and right hip joint (average of three measurements in each joint as described above) was used.

One senior rheumatologist (A.I.) with extensive experience in X-ray assessment and one fellow (M.K.) with specific interest in AS research performed a blinded radiographic review of X-ray pairs. Intraobserver and interobserver reliability was established using intraclass correlation coefficients (ICC). Both readers achieved excellent agreement for BASRI-h scores and the three points of intra-articular distance (ICC=0.88; 95 % CI, 0.85, 0.91) in anteroposterior X-rays of the pelvis. Paired *t* test was used to compare the mean differences. Statistic analysis was performed using STATA 11.0.

## Results

As shown in the Table 1, patients' mean age at baseline was  $44.5 \pm 12$  years; these patients had a relatively young age at onset ( $28.5 \pm 10.8$  years) with an average disease duration of  $16 \pm 11$  years. Patients' functional status at baseline, accessed by BASFI, correlated negatively with average joint space width (Spearman  $r = -0.5$ ,  $P = 0.007$ ) and positively with BASRI-h score (Spearman  $r = 0.49$ ,  $P = 0.02$ ); no correlation was observed between average joint space width and disease activity measurements (BASDAI, CRP) or patients' age and disease duration.

**Table 1** Demographic and descriptive characteristics of 23 patients with AS. Values are given as mean±SD (range)

	Baseline	End of follow-up
Age (years)	44.5±12 (22–68)	51.6±13 (27–77)
Disease duration	16±11 (2.7–40)	22±12.5 (7–47)
Years of infliximab treatment	0	6±2.5 (2–10)
BASDAI	6.3±1.25 (3.5–8.4)	1.67±1.3 (0.2–4.2)
BASFI	6.9±1.9 (3.3–10)	3.3±1.8 (1.2–8)
BASRI hip score	2.5±0.86 (1–4)	2.5±0.86 (1–4)
Average of mean joint space width in both hips (mm)	3.56±0.7 (2.4–5.33)	3.59±0.79 (2.25–5.33)

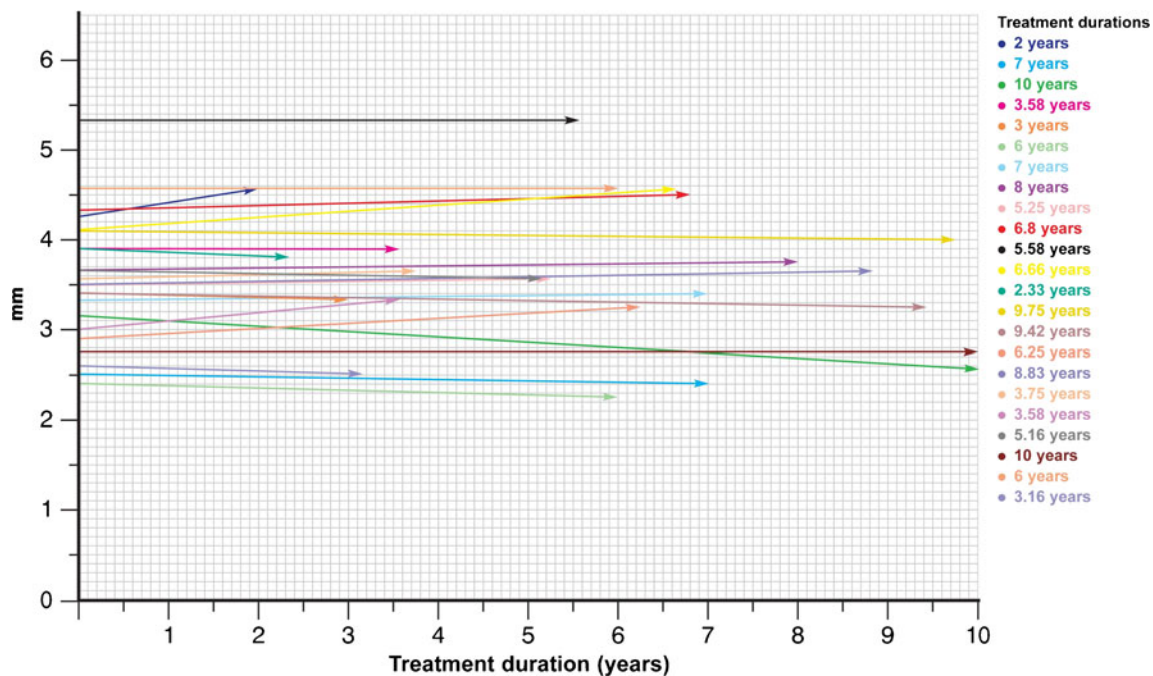
Infliximab was given as monotherapy during the whole follow-up period in 21 patients, whereas methotrexate was added in one patient due to inadequate response (HACAs not measured), as well as in a second patient with knee arthritis. Overall, after 6±2.5 years of infliximab treatment, there was a remarkable improvement in disease activity assessed by BASDAI (6.3±1.25 versus 1.67±1.3, *P*<0.0001) and CRP (21.6±12.3 versus 5.8±4.3 mg/l, *P*<0.0001), as well as in functional status assessed by BASFI (6.9±1.9 versus 3.3±1.8, *P*<0.0001) (Table 1).

Analysis of anteroposterior X-rays of the pelvis at baseline revealed that the mean BASRI-h score was 2.50±0.86, being 1 in 7 hips, 2 in 16 hips, 3 in 16 hips, and 4 in 7 hips (including

two arthroplasties). Individual BASRI-h scores remained unchanged in all hips after 2–10 years of infliximab treatment (6±2.5 years) (Table 1). Moreover, as shown in Fig. 2, the average width of the whole joint space at baseline (3.56±0.7mm, *n*=44) remained unchanged during 6±2.5 years of continuous infliximab treatment in these patients (3.59±0.79 mm). Notably, the mean joint space width of the right (3.6±0.7 versus 3.6±0.85 mm, *n*=23) and left (3.4±0.68 versus 3.45±0.75mm, *n*=21 [two arthroplasties are excluded]) hips remained unchanged.

**Discussion**

Whether the osteoproliferation that characterizes AS depends on inflammation is currently a matter of debate [12]. However, osteodestruction in inflammatory rheumatic diseases is thought to be tightly connected to TNF-mediated pleiotropic actions [13]. Along this line, and despite the lack of a historical control group which is the major limitation of our study, the findings presented herein suggest that continuous anti-TNF treatment with infliximab for up to 10 years inhibits radiographic progression of hip arthritis in clinically responding patients with AS. To the best of our knowledge, similar results have not appeared in the literature so far. As Lian et al. reported, treatment with etanercept combined with MTX significantly improved disease activity in AS patients with hip joint involvement and inhibited radiographic progression [14]. However,



**Fig. 2** Patients’ hip joint width after 6±2.5 years of infliximab treatment: individual patient’s average joint width of both hips (in millimeter) in anteroposterior X-rays obtained at baseline and at end of follow-

up in 23 patients with AS treated with infliximab. The whole joint space was estimated by three distinct measurements of interbone distance in each hip as described in “Patients and methods”

this study included a rather short follow-up period of 12 months, whereas in AS a time frame of at least 2 years is required for radiographic changes to occur [15].

Our long-term data suggest that the positive effect of anti-TNF treatment on osteodestructive changes seen in patients with RA [6] is also observed in patients with AS. Preliminary cohort data suggesting a lower incidence of hip replacements in patients with AS over the past few years, potentially due to the effect of anti-TNF agents [16], are in line with the findings of our observational study, in which only patients responding to anti-TNF treatment are included. Moreover, the significant association between BASFI score and the hip joint space width clearly denotes the contribution of hip arthritis to functional impairment in AS patients. It should be mentioned that in three other infliximab-treated patients with hip involvement from our AS cohort, who were not included in this study, a prominent radiographic deterioration of hip arthritis was noted after discontinuation of infliximab due to the diagnosis of neoplasia.

To conclude, therapeutic inhibition of TNF treatment seems to result in arrest of radiographic progression in AS patients with hip arthritis. Prospective controlled studies need to confirm a possibly differential effect of these agents on radiographic progression of spinal versus extraspinal manifestations of the disease.

**Disclosures** None.

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