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High prevalence of hip involvement and decrease in inflammatory ultrasound lesions during tumour necrosis factor-α blocking therapy in ankylosing spondylitis

Freke Wink¹, Suzanne Arends², Fiona Maas², Hendrika Bootsma², Ed N. Griep³, George A. W. Bruyn⁴ and Anneke Spoorenberg²

Abstract

Objectives. To assess the prevalence of clinical, US and radiographic hip involvement in AS patients with active disease and to explore the associations between these assessments. Furthermore, to evaluate the effect of 6 months of TNF-α blocking therapy on tender and inflammatory power Doppler US lesions of hip joints.

Methods. Consecutive AS patients starting TNF-α blocking therapy were evaluated for hip joint involvement. At baseline, patient-reported history of hip involvement was assessed and radiographic evaluation (BASRI-hip) was performed. Clinical examination (tender hip joints) and US examination took place before and after 6 months of treatment.

Results. Of the 111 included patients, 20% reported a history of hip involvement. At baseline, tender hip joints were present in 23% of patients. US examination showed inflammatory lesions in 17% of patients, of which 74% had positive power Doppler. Structural lesions were present in 20% of patients, of which 55% had osteophytes. Structural radiographic damage was seen in 10% of patients. Highest concordance was found between history of hip involvement and radiographic hip involvement (phi coefficient 0.333). After 6 months of TNF-α blocking therapy, significant decrease was found in tender hip joints (from 29 to 11), total number of inflammatory US lesions (from 29 to 9) and positive power Doppler (from 22 to 6).

Conclusion. The prevalence rate of hip involvement in AS patients varies from 10 to 23%, depending on the type of hip assessment. TNF-α blocking therapy significantly improved tender hip joints, and inflammatory US lesions including positive power Doppler.

Key words: ankylosing spondylitis, hip involvement, ultrasonography, TNF-α blocking therapy
synovitis, degeneration of the coxo-femoral joint may occur.

There are several methods to evaluate hip involvement in axial SpA. Most often patient-reported symptoms, physical examination and, if indicated, radiographs of the hip joints are used. Clinically, it is often very difficult to distinguish symptoms related to inflammatory or to degenerative hip lesions. Musculoskeletal US can be of supplementary value to differentiate between these lesions. US is a dynamic and versatile imaging technique that has proven to be valuable in detecting early inflammation of synovial joints [4]. In RA, it has been shown that US is more sensitive in detecting inflammation in comparison to physical examination [5]. Furthermore, US with power Doppler has proven to be reliable for qualitative grading of the vascularity of synovial tissue of the hip [6].

The use of US for the evaluation of hip involvement has been investigated in only a limited number of studies in AS. In a cross-sectional study including 56 AS patients of which 80% were treated with TNF-α blocking therapy, moderate correlations were found between clinical parameters such as hip tenderness and US abnormalities of the hip joint [7]. In a subgroup consisting of 39 AS patients with no sign or symptoms of hip involvement, US abnormalities were significantly related to higher CRP levels [7]. Unfortunately, no further information was given on which US abnormalities were found in this subgroup. Currently, there is no international consensus on the best method to assess hip involvement in AS [3]. Also, the recent update of the Assessment of SpondyloArthritis international Society-EULAR recommendations on management of axial SpA lacks advice on how to assess hip involvement [8]

Although clinical trials have shown excellent efficacy of TNF-α blocking therapy in axial SpA [9–12], limited evidence is available regarding its effect on hip involvement. Two Chinese studies on hip involvement in AS patients showed significant clinical improvement using the Harris hip score after 3 months of treatment with etanercept combined with methotrexate [13, 14]. A retrospective study of 23 AS patients treated for 2–10 years with infliximab showed that radiographic progression of hip involvement stabilized after 6 ± 2.5 years [15], which is similar to several results concerning the effect of TNF-α inhibitors on long-term radiographic progression of the spine [16, 17]. So far, no data are available regarding the effect of TNF-α blocking therapy on inflammatory hip lesions assessed with US.

Therefore, our aim was to investigate the prevalence of hip involvement using clinical, US and radiographic evaluation in AS patients with active disease, and to explore the mutual associations between these different assessments. Furthermore, we sought to evaluate the effect of TNF-α blocking therapy on tender hip joints and inflammatory US lesions in these patients.

Methods

Patients

Between November 2004 and October 2008, all consecutive outpatients with AS who started TNF-α blocking therapy at the Medical Center Leeuwarden were included in this study. All patients participated in the Groningen Leeuwarden Axial SpA cohort, a prospective longitudinal observational cohort study with follow-up visits according to a fixed protocol [18]. All patients were over 18 years of age, fulfilled the modified New York criteria for AS and started TNF-α blocking therapy because of active disease (BASDAI ≥ 4 and/or expert opinion) according to the Assessment of SpondyloArthritis international Society consensus statement [19].

The Groningen Leeuwarden Axial SpA cohort was approved by the local ethics committees of Medical Center Leeuwarden and University Medical Center Groningen. All patients provided written informed consent according to the Declaration of Helsinki.

Assessments of hip involvement

Hip involvement was assessed with four different methods. At baseline, patients were asked for history of hip involvement (yes/no) and radiographical lesions of both hip joints were scored using the BASRI-hip (score 0–4) [20]. Clinical evaluation of tender hip joints during physical examination (yes/no) and US examination were performed at bilateral hip joints at baseline and after 6 months of treatment.

US protocol

Complete US examinations of the hip joints in brightness and power Doppler mode were performed by two rheumatologists (G.A.W.B., E.N.G.), experts in the field of ultrasonography. The US examiners were blinded to clinical data such as disease status and previous results of the US examination. US examinations at baseline and 6 months were performed by the same investigator.

Patients were instructed to discontinue the use of NSAIDs a week before both US examinations, because of the potential effect on inflammatory lesions. An Esaote Technos MPX US machine (Esaote, Genoa, Italy) equipped with a 3.5–5 MHz convex transducer was used.

US examination was conducted according to a specific scanning protocol dedicated to practical use in daily clinical practice. The hip joints were assessed bilaterally in two orthogonal planes. In brightness mode, hip joints were scored for the following abnormalities: effusion, erosions/irregular cortex, osteophytes and calcifications. The definition of effusion was ultrasonographic distance between the joint capsule and the femoral shaft >7 mm, as described by Koski [5]. The combination of osteophytes and erosions/irregular cortex was considered as generalized osteoarthritis/degenerative changes. In addition, hip joints were scanned for increased vascularisation by power Doppler mode. Doppler settings were as follows: a Doppler frequency of 6.3 MHz with a low wall filter, and pulse repetition frequency of 750 KHz. Gain was adjusted until background noise was removed.

All abnormalities, including positive power Doppler, were scored as absence (0) or presence (1). Bone erosions/irregular cortex, osteophytes and calcifications were considered as structural lesions. Effusion and
positive power Doppler were considered to be inflamatory lesions.

**BASRI-hip**

Antero-posterior radiographs of the pelvis were scored by two trained independent readers blinded to patient characteristics (F.M. and Rizwana N. Chaudhry). Radiographs were scored for five severity grades: 0 = no change (normal), 1 = possible focal joint space narrowing (suspicious), 2 = definite narrowing, leaving a circumferential joint space >2 mm (minimal), 3 = narrowing but circumferential joint space <2 mm or bone-on-bone apposition <2 cm (moderate), 4 = bone deformity or bone-on-bone apposition >2 cm or 5 = total hip replacement (severe). The BASRI-hip score of patients was reassessed if the BASRI-hip showed discrepancy under and above the overall 95% limits of agreement. A third independent reader reassessed the radiographs and the score of the first or second reader closest to the third reader was used. The average BASRI-hip score was used for the analysis. Inter-observer reliability for the presence of hip involvement was very good with Cohen’s κ of 0.83 and percentage of absolute agreement of 97%. BASRI-hip ≥ 2 was defined as radiographic hip involvement.

**Other clinical assessments**

Overall disease activity was assessed with the BASDAI and the ASDAS. Furthermore, CRP and ESR were measured. Spinal radiographic damage was scored by two trained independent readers blinded to patient characteristics using the modified Stoke AS Spine Score with a very good intra-class correlation coefficient (0.98) [17].

**Statistical analysis**

Prevalence rates were expressed as number of patients or lesions (%). Normally distributed data were reported as mean ± s.d. and non-normally distributed data as median (range).

Independent samples t test, Mann–Whitney U test, χ² test and Fisher Exact test were used to compare baseline characteristics between patients with and without complete power Doppler US examination. Phi coefficients and percentage concordance were calculated to investigate the mutual association between the different assessments of hip involvement. Wilcoxon Signed Rank test and McNemar test were used to compare clinical and power Doppler US parameters at baseline and after 6 months. P-values ≤ 0.05 were considered as statistically significant. Statistical analysis was performed using PASW Statistics 22 (SPSS, Chicago, IL, USA).

**Results**

In total, 111 consecutive AS patients starting with TNF-α blocking therapy were included. All patients underwent US examination at baseline and 85 patients had a second US examination after 6 months of treatment. Baseline BASRI-hip was available for 99 patients.

The mean age of all patients was 42.9 years (s.d. ±10.9), 71% were male, median symptom duration was 15 years (range 2–49) and 81% were HLA-B27 positive. Baseline characteristics, including disease activity, were comparable between patients with and without US examination at both time points, except for symptom duration and time since diagnosis, which were longer for the patients with US examination at both time points (17 vs 8 years, P < 0.001 and 9 vs 3 years, P < 0.005). All patient characteristics are shown in Table 1.

**Prevalence of hip involvement**

At baseline, patient-reported history of hip involvement was present in 22 (20%) patients and 25 (23%) patients had one or more tender hip joint during physical examination. Of these 25 patients, 8 (32%) reported that both hip joints were tender (Table 2).

In total, at baseline 68 US lesions of the hip joints were found in 33 (30%) patients. Of these 68 lesions, 38 (56%) were structural and 30 (44%) were inflammatory lesions. The structural lesions were present in 22 (20%) patients, which were bilateral in 12 patients. The structural lesions mainly consisted of osteophytes. Inflammatory lesions

| TABLE 1 Baseline characteristics of the AS study population (n = 111) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Gender (male) (n, %) | 79 (71) | Age, years | 42.9 (10.9) | Duration of symptoms, years | 15 (2–49) | Time since diagnosis, years | 7 (0–37) | HLA-B27+ (n, %) | 90 (81) | History of psoriasis (n, %) | 9 (8) | History of IBD (n, %) | 11 (10) |
| History of uveitis (n, %) | 31 (28) | History of peripheral arthritis (n, %) | 36 (32) | mSASSS score (range 0–72) | 9.0 (72) |
| MASES (range 0–13) | 2 (12) | MASES ≥ 1 (n, %) | 85 (77) | BASDAI (range 0–10) | 6.0 (8–9.2) | BASDAI ≥ 4 (n, %) | 100 (90) | ASDASgi (n, %) | 3.8 (1.7–5.9) | ASDASgi ≥ 2.1 (n, %) | 108 (97) |
| CRP, mg/l | 15 (2–99) | CRP ≥ 5 (n, %) | 93 (84) | ESR, mm/h | 22 (2–90) |

Values are mean ± s.d. or median (range) unless otherwise indicated. HLA-B27+: HLA B27 positive; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.

| TABLE 2 Prevalence of hip involvement with different assessments |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| History of hip involvement | 22 (20) | Tender hip joints | 25 (23) | US evaluation inflammatory lesions | 19 (17) | US evaluation structural lesions | 22 (20) | Radiographic assessment | 11 (10) |

Values presented as number of patients (%).
were found in 19 (17%) patients of which 8 patients showed bilateral involvement. Positive power Doppler was the most prevalent inflammatory lesion (Table 3).

Structural radiographic damage of at least one hip joint, defined as a BASRI-hip score of at least $\geq 2$, was seen in 11 (10%) patients (Table 2). In three patients this structural radiographic damage was bilateral.

**Associations between assessments of hip involvement**

Moderate correlation between history of hip involvement and radiographic hip involvement was found (Phi coefficient 0.333, $P < 0.05$), with also the highest positive agreement. Structural US lesions showed weak correlation with radiological hip involvement (Phi coefficient 0.203, $P < 0.05$) and tender hip joints (Phi coefficient 0.193, $P < 0.05$). No significant correlation was found between all other assessments. The concordance rates were relatively high due to the relatively large number of hip joints without abnormalities (Table 4). Only two of the patients with inflammatory US lesions reported also a painful hip (supplementary Table S1, available at *Rheumatology* online).

**Effect of TNF-$\alpha$ blocking therapy**

The number of tender hip joints decreased significantly from 29 at baseline to 11 after 6 months of TNF-$\alpha$ blocking therapy. Also, the percentage of patients with tender hip joints showed a significant decrease from 25 to 12% ($P < 0.05$).

US examination of hip joints showed a significant decrease in total number of inflammatory lesions from 29 at baseline to 9 after 6 months of therapy. The number of positive power Doppler lesions decreased significantly from 22 to 6 and presence of effusion decreased from 7 to 3 ($P < 0.5$).

The percentage of patients showing one or more inflammatory lesion at baseline decreased significantly from 21 to 7% after 6 months of TNF-$\alpha$ blocking therapy ($P < 0.05$). Also, the percentage of patients with positive power Doppler signal of hip joints decreased significantly from 16 to 6% ($P < 0.05$) (Table 5).

**Table 3** Prevalence of US abnormalities at the hip joints in AS patients at baseline ($n = 111$)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total inflammatory</td>
<td>19</td>
</tr>
<tr>
<td>Effusion</td>
<td>8</td>
</tr>
<tr>
<td>Positive power Doppler</td>
<td>14</td>
</tr>
<tr>
<td>Total structural</td>
<td>22</td>
</tr>
<tr>
<td>Erosion/irregular</td>
<td>3</td>
</tr>
<tr>
<td>Osteophyte</td>
<td>12</td>
</tr>
<tr>
<td>Calcifications</td>
<td>2</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 4** Correlations (Phi coefficient) and concordance rates (%) between assessments of hip involvement (222 hip joints)

| Assessment | Tender hip joints | Inflammatory US lesions | Structural US lesions | BASRI hip score $\geq 2$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td>0.076</td>
<td>-0.106</td>
<td>0.046</td>
<td>0.333*</td>
</tr>
<tr>
<td>CR (%)</td>
<td>70</td>
<td>81</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>PA (%)</td>
<td>28</td>
<td>11</td>
<td>23</td>
<td>67</td>
</tr>
<tr>
<td>Tender hip joints</td>
<td>0.081</td>
<td>0.193*</td>
<td>-0.123</td>
<td></td>
</tr>
<tr>
<td>CR (%)</td>
<td>74</td>
<td>78</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>PA (%)</td>
<td>11</td>
<td>43</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Inflammatory US lesions</td>
<td>0.057</td>
<td>0.040</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (%)</td>
<td>74</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA (%)</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural US lesions</td>
<td>0.203*</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td>74</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (%)</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA (%)</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $P < 0.05$. PC: Phi coefficient; CR: concordance rate; PA: positive agreement.
Discussion

In this prospective observational cohort study, hip involvement in AS patients with active disease was assessed with four different methods: patient-reported history of hip involvement, clinical evaluation of tender hip joints, US examination of inflammatory and structural lesions, and radiological assessment. Furthermore, the effect of TNF-α blocking therapy on tender hip joints and inflammatory US lesions was evaluated after 6 months. As far as we know, this is the first study in which the different assessments of hip involvement and the effect of TNF-α blocking therapy have been investigated in the same group of patients.

In the present study, the prevalence rate of patient-reported history of hip involvement was 20%, whereas 23% experienced at least one tender hip joint during physical examination. Vander Cruysen et al. [2] analysed 1405 Spanish (selection from the REGISPONSER cohort with definite AS) and 466 Ibero-American (selection from the RESPONDIA cohort with definite AS) AS patients for clinical hip involvement and prevalence rates of 24 and 36%, respectively, were found in these cohorts. Clinical hip involvement was defined as pain or limitation of the hip joints. Unfortunately, no data on the overall disease duration, disease activity and treatment of the included patients were reported, which makes it difficult to place these data into perspective.

There is no standardized uniform definition of clinical hip involvement available and it is most frequently described as the clinical perception of the rheumatologist [3]. It is debated whether hip involvement is clinically best-evaluated by symptoms, physical examination (for instance internal rotation of the hip) or a combination (Harris hip score). Since there is no consensus this may lead to heterogeneous results and thus variable prevalence rates.

US is a more advanced technique of assessing hip involvement. In AS, little is known on US evaluation of hip joints. However, overall US examination of hip joints has been shown to be more sensitive for finding hip abnormalities than clinical evaluation and conventional radiographs, especially in early and juvenile RA [21–23].

In total, 30% of our AS patients showed US lesions of hip joints, which were stratified into inflammatory and structural lesions. Of the inflammatory US lesions, positive power Doppler was observed in almost 13% of the patients and effusion was found in 7%. Compared with previous reported data this is somewhat surprising. Sakellariou et al. [7] found synovial hypertrophy in 16% of patients with no detectable power Doppler signal and joint effusion was found in almost 27% of the patients. This difference might partly be explained by the high disease activity status of our patients in contrast to the low disease activity status of the patients described by Sakellariou et al. (BASDAI 6.0 vs 2.65 and CRP 15 vs 3 mg/L). Moreover, 80% of their patients were already treated with TNF-α inhibitors in comparison with none of our patients. In AS patients with a high disease activity status more hyperaemia of inflammatory synovial tissue might be expected. An even stronger contributory explanation may be that Esaco US machines are more sensitive to microflow than other machines, which possibly adds to the relatively high prevalence of positive power Doppler in our study [24].

Structural damage of hip joints was evaluated with US and radiographs. Twenty-two percent of AS patients showed structural US lesions, whereas only 10% showed radiographic hip involvement using the BASRI-hip score of ≥2. This prevalence rate of radiographic hip involvement is comparable to the prevalence of 9% found in found in 531 Taiwanese AS patients with also a BASRI-hip score of ≥2 [25]. Calin and Elswood [1] found a higher prevalence rate of radiographic hip involvement (grade 2–4) of 20% in 92 AS patients. Their study was published in 1988, an era in which treatment options were less extensive and effective than the current possibilities, possibly resulting in more structural hip damage. This might have resulted in a higher prevalence rate compared with our recent study.

The differences in prevalence rates of structural hip lesions assessed with radiographs or US suggests that US evaluation of hip joints is more sensitive in detecting structural lesions than radiographs. Although the BASRI-hip score is well established for the assessment of radiographic hip involvement, definite radiographic damage is demonstrated in a relatively late stage. Furthermore, radiographic scores focus mostly on joint-space narrowing, whereas US especially informs on osteophytes and cortical bone abnormalities. This also explains the weak correlation between the BASRI-hip and the structural lesions on US.

Hip involvement in an earlier stage of the disease, characterized by inflammation, can be visualized only by US or MRI. This is confirmed by MRI studies in AS which showed that MRI is more sensitive in assessing hip involvement than a radiograph of the pelvis, especially in early disease [26, 27]. However, compared with US, disadvantages of MRI are the limited availability and high costs.

In the present study, we only found a moderate correlation between the history and radiographic hip involvement. All other correlations were weak, implying that the different assessments seem to measure different aspects of hip involvement. Strikingly, no correlation was found between painful hip joints and inflammatory US lesions, suggesting that inflammatory lesions, including positive power Doppler, may be present without accompanying hip complaints. In our population, 19 out of 111 AS patients with active disease had inflammatory US lesions at one or both hip joints. Only 2 of these 19 patients also reported an accompanying painful hip joint. Also, in RA and juvenile RA US abnormalities also were found in patients with no or only mild symptoms of hip involvement [21, 23].

Little is known about the effect of TNF-α blocking therapy on hip involvement in AS. Data from the Norwegian Arthroplasty Register demonstrated that hip replacement surgery in AS patients treated with TNF-α blockers occurs less frequent and at older age than before the introduction...
of this therapy [28]. Additionally, a retrospective study showed that radiographic progression of hip involvement stabilized during 2–10 years of treatment with infliximab [15]. This might suggest that TNF-α blocking therapy has some effect on the development of structural damage of hip joints in AS patients, but more longitudinal data are necessary to prove this.

Additional to these results, our observational study is the first that showed also significant improvement in the total number of inflammatory US lesions and positive power Doppler signal at the hip joints after 6 months of treatment with TNF-α blocking therapy in AS patients.

In summary, this observational cohort study in daily clinical practice showed relatively high prevalence rates of hip involvement in AS patients with active disease varying from 10 to 23%, depending on the assessment used. The varying assessments of hip joint involvement measure different aspects of joint involvement. US lesions were frequently found and inflammatory lesions were not related to patient reported painful hips. Importantly, inflammatory US lesions and positive power Doppler signal at the hip joints decreased significantly after 6 months of TNF-α blocking therapy. Therefore, based on our results, US examination of hip joints is an useful, sensitive and objective method that contributes to the assessment of hip involvement in AS in daily clinical practice, including the evaluation of the response of TNF-α blocking therapy on inflammatory lesions.

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Supplementary data

Supplementary data are available at Rheumatology online.

References


