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Full Length Research Paper

The Role of Musculoskeletal Ultrasound scanning of axial and peripheral joints of Ankylosing Spondylitis patients in short-term monitoring response to TNF-α antagonist therapy: Clinical Trial

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Background: **Although musculoskeletal Ultrasound (MSK US) allows visualization of peripheral arthritis and enthesitis, its role in the assessment of axial manifestations remain minimal. Few recent studies used duplex and color Doppler to detect synovitis in sacroiliac joint in Ankylosing Spondylitis (AS).** ***Objective:*** **This study aims to evaluate the value of MSK US scanning of both axial and peripheral arthritis as well as enthesitis in AS patients in short-term monitoring response to TNF-α antagonist therapy and to detect the best prognostic predictors of good response to treatment.** ***Methods:*** **Twenty patients with ankylosing spondylitis, diagnosed according to Modified 1984 New York criteria. Clinical assessment of axial , peripheral joints and enthesis with emphasis on disease activity with BASDAI, ASDAS-CRP and BASMI. Imaging by plain X-rays of spines and S.I joints using BASRI score and by US using SOLAR score for sacro-iliac (S.I), hip and knee joints as well as four sites of enthesis. These regions were assessed by grey scale US (GSUS) and power Doppler US (PDUS) according to EULAR guidelines. All patients were assigned to anti TNFα therapy for 6 months then clinical and imaging re-assessment were done.** ***Results:*** **Twenty patients with AS (18 males and 2 females), their mean age was 34.3± 9.5261, mean disease duration was 9.65 ±4.3682, mean BASDAI was 7.225± 1.2191 and ASDAS CRP was 4.205± 0.620 with evidence of active sacroiliitis, hip and knee synovitis as well as increased plantar fascia (PF) and tendo Achillis (TA) thickness by GSUS and PDUS. After six months of anti TNFα therapy, all patients were significantly improved regarding BASDAI, BASMI, GSUS of knee, TA and PF thickness (t= 9.234, t = 3.911, t= 10.258, t= 6.948, t= 8.076, p <0.01) respectively as well as S.I synovitis by PDUS (p< 0.05). To elaborate efficacy of treatment after 6 months, we measured major clinical response by BASDAI 50% and clinically important improvement by Δ ASDAS ≥1.1, and we noticed that Δ ASDAS ≥1.1 was significantly correlated with age, peripheral arthritis, baseline BASDAI, BASMI, ESR, number of enthesis, BASRI total and S.I and hip synovitis (p <0.05). Also, we noticed that baseline high ESR and increased number of enthesis as well as initial ASDAS >2.1 and PF thickness > 4mm were best predictors of good response to anti TNFα therapy.** ***Conclusion:*** **MSK US is considered a promising tool for assessing axial ,peripheral arthritis and enthesopathy in AS patients and effectively help in monitoring short term effect of anti TNFα therapy**

Keywords: Ankylosing spondylitis, US scanning , sacroiliitis, enthesopathy, anti TNF-α, therapy

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease affecting about twice as many men as women, with an estimated prevalence of 0.2–0.8% (Braun and Sieper, 2007). The first symptoms normally occur in the second and third decade of life. (Reveille 2011, Feldtkeller et al., 2003). AS typically involve the axial skeleton in the form of spine (46.6%), followed by enthesitis (9.8%) and dactylitis (1.9%). (Sieper et al., 2002). Enthesitis is considered as the primary anatomical

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lesion in ankylosing spondylitis (AS). Moreover, Disability in SpAs is generally due to spinal entheseal, new bone formation (McGonagle, 2003).

Imaging in ankylosing spondylitis (AS) has been synonymous for decades with conventional radiography (CR). However, developments in computed tomography (CT), ultrasonography (US) and particularly magnetic resonance imaging (MRI) have dramatically increased the amount and scope of information obtainable by imaging (Ostergaard and Lambert, 2012). By using CT, sclerosis and ankylosis can easily be diagnosed, and for the detection of bony changes, CT can be superior to MRI. However, MRI also identifies abnormalities thought to reflect inflammatory disease activity in the joint and subchondral bone ,especially early in the course of the disease (Inanc et al., 2005) . The availability of MRI, however, is limited. The technique is time consuming and costly and may not be applied to all patients with inflammatory low back pain and suspected sacroiliitis in clinical practice. (Braun et al., 2000). Musculoskeletal US is a well-established imaging method that is routinely used in daily practice by numerous rheumatologists, for both evaluating disease activity and monitoring therapy in Rheumatoid arthritis (Backhaus et al., 2009).

As demonstrated in small joints, GSUS and power Doppler US (PDUS) exhibit a higher sensitivity in detecting inflammation of large joints compared with clinical examination (Luukkainen et al., 2007; Naredo et al., 2002).

In 2012, the sonography of large joints in Rheumatology (SOLAR) score is a valuable tool for the quantitative and qualitative evaluation of large joint involvement and monitoring treatment response in patients with RA using US. (Hartung el al., 2012). Despite this fact, no US score for large joint involvement has been yet used for PsA and AS, until Shafer and colleagues, (2013) introduced SOLAR score in a cohort of patients with Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS). They reported as a conclusion the SOLAR is a very suitable instrument for the qualitative and quantitative evaluation of large joint involvement in PsA and AS patients and allows for treatment monitoring. Compared with clinical examination, grey scale ultrasound (GSUS) and power Doppler US (PDUS) are more sensitive method for detecting synovitis and tenosynovitis. Although Ultrasonography allows visualization of peripheral arthritis and enthesitis, its role in the assessment of axial manifestations remain minimal. However, it has been shown previously that contrast-enhanced color Doppler ultrasound compares favorably with MRI in its ability to demonstrate SI joint inflammation (Klauser et al., 2005). (PDUS) is theoretically more sensitive to flow and independent of the angle of insonation (Klauser et al., 2005). Few recent studies used duplex and color Doppler to detect synovitis in sacroiliac joint in AS (Unlu, Pamir and Cakir, 2007; Zhu et al., 2012). For over 5 decades the mainstay of therapy of AS has been long-term use of NSAIDs in combination with traditional disease modifying antirheumatic drugs (DMARDs) including methotrexate and sulfasalazine may improve peripheral arthritis and sulfasalazine may have a modest benefit for inflammatory back pain in patients with relatively mild disease (Zochling et al., 2006). The cytokine TNF-α is regarded as an important mediator in the disease process and raised levels of TNF have been found in the SI joints of patients with AS (Francois et al., 2006). In this context, treatment of AS with biological agents which block tumor necrosis factor alpha (TNFα) has been a key therapeutic advance. Many trials using anti TNFα medications (Etanercept, Infliximab, and Adalimumab) as a treatment for AS, and the Outcome measures commonly used in trials of therapy were clinical outcomes (Barkham et al., 2005). Previous trial using Etanercept as a treatment for AS, improvements over base-line values for various measures of disease activity, including morning stiffness, spinal pain, functioning, quality of life, enthesitis, chest expansion, erythrocyte sedimentation rate, and C-reactive protein (Zochling et al., 2006; Konttinen et al., 2007; Gadsby e, Deighton, 2007).

Objective

This study aims to evaluate the value of MSK US scanning of both axial and peripheral arthritis as well as enthesitis in Ankylosing Spondylitis patients in short-term monitoring response to TNF-α antagonist therapy and to detect the best prognostic predictors of good response to treatment.

PATIENTS AND METHODS

Twenty patients with ankylosing spondylitis; who were diagnosed according to Modified 1984 New York criteria; were included in this study. Participants were collected from outpatients clinics of Physical Medicine, Rheumatology and Rehabilitation Department of Ain Shams University Hospital.

Inclusion criteria for appropriate AS patients for anti TNFα therapy were: AS patients had active axial and peripheral involvement, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores ⩾ 4, physician global assessment > 2 on Likert scale and patients who were unresponsive to > 1 DMARDS (Sulfasalazine, Methotrexate) and> 2 NSAIDS for more than 3 months. (Braun et al., 2011). All patients were designed to receive TNF α inhibitors: Etanercept, Adalimumab and Infliximab monotherapy or combined with MTX, for 6 months duration.

Patients with a history of malignancy, active or latent tuberculosis, women in pregnancy or lactation; or were receiving high-dose steroids, (>10 mg prednisolone) or had current infections were excluded from this study.

Each patient gave his written informed consent for participation of the study. The study was conducted in accordance with the World Medical Association Declaration of Helsinki for human subjects and was approved by the ethics committee of Faculty of Medicine, Ain Shams University.

All patients underwent full medical history and clinical examination at baseline and 6 months after receiving TNFα inhibitors by two expert rheumatologists with emphasis on disease activity with BASDAI (Garrett et al., 1994) and ASDAS-CRP. ASDAS-CRP is an algorithm comprising 3 BASDAI questions, the patient global assessment, and CRP. ASDAS ≥ 1.3 <2.1 indicates moderate, ≥ 2.1 < 3.5 indicate high, and ≥ 3.5 indicates very high disease activity (Machado et al., 2011). Patients were examined for axial and peripheral arthritis, as well as for enthesopathy. SI joint activity was determined clinically as previously reported (Rudwaliet et al., 2006). Clinical assessment included SI joint mobility, pain provocation tests as lateral pelvic compression, prone sacral pressure, pressure over the second sacral foramen, upward pressure on the ischial bone, and superior iliac glide test.

Palpation the four sites of enthesis (Achillis tendons (AT) and retrocalcaneal bursa, Patellar tendon (PT), greater trochanter (GT) and Plantar fascia (PF)) in both sides for tenderness and swelling as a sign of enthesopathy.

Other metrology tests including chest expansion were done and the Bath Ankylosing Spondylitis metrology index (BASMI) was calculated (Jenkinson et al., 1994).

CBC, ESR and CRP levels, liver function (AST, ALT) and kidney function (BUN, serum creatinine) were recorded. Plain radiography of cervical and lumbar spines and both sacroiliac joints were performed at baseline and 6 months post treatment using The Bath Ankylosing Spondylitis Radiology Index (BASRI) for spines and sacroiliac joints (MacKay et al., 1998). BASRI for CS and LS: the scoring is from 0-4 (for normal, suspicious, mild, moderate, and severe). For Sacroiliac joints: A-P radiographs of the right and left sacroiliac joints are scored according to the New York criteria (Dale, 1979):0= no disease; 1= suspicious; 2= mild; 3= moderate; 4= severe.

The CS, LS and S.I scores were added to get BASRI total (2-12) Scoring of BASRI total (2-12) was conducted by two, centrally trained, independent readers who were blinded to treatment information and radiograph sequence, and scores were averaged between the two readers for analysis. All patients underwent US scanning of both sacroiliac, hip and knee joints as well as both tendo Achillis and retrocalcaneal bursa, plantar fascia, patellar tendons at tibial tuberosities and greater trochanter ligaments. Using Logiq 9 ultrasound equipment from GE (General Electric Healthcare, Chalfont St Giles, UK) with a linear array transducer (9L) working with 9-13 MHz frequency for grey scale settings. Power Doppler (PD) settings were standardized with a pulse repetition frequency of 750 Hz, a color-mode frequency of 9.1 MHz and low wall filters. The color gain was increased to the highest value not generating PD signals under the bony cortex. The mentioned joints were examined semi quantitatively using sonography of large joints in Rheumatology) (SOLAR) score according to the German and European League against Rheumatism (EULAR) guidelines (Schafer et al., 2013) at baseline and the follow up visits. All joint regions were assessed by grey scale US (GSUS) and power Doppler US (PDUS). GSUS for synovitis, tenosynovitis, and bursal enlargement at selected joints was analyzed semi quantitatively from 0 to 3 (0 = absence, 1 = mild, 2 = moderate, 3 = severe. Synovial, tenosynovial, AT, PF and intrabursal blood flow were evaluated by PDUS and were scored semi quantitatively (grade 0–3) by PDUS.

The GSUS score for the knee range from 0-12 by scanning four areas of the knee, the suprapatellar longitudinal, the medial longitudinal, the lateral longitudinal, and the posterior region, each for a grade from 0 to 3. In PDUS we scored the same areas of the knee adding an additional infrapatellar longitudinal scan and grading it from 0 to 3, yielding a total possible score of 15. The GSUS /PDUS scores for the hip joint range from 0- 3 , using the anterior longitudinal scan.

For Sacroiliac joints: synovitis, irregularity, joint narrowing and altered echogenicity were detected by GSUS with a score (0-1) 0= absent, 1= present (Bandinelli et al., 2013) and by color Doppler US, CDUS examination was performed to detect vascularization, which was defined as color-flow signals in the area of the SI joints (Klauser et al., 2005).

In sacroiliac joints scanning: The patients were examined in the prone position. The transducer was settled to the sacral region from the posterior aspect in the transverse position, according to a scanning technique previously proposed (Klauser et al., 2008). The SI joint was observed as a hypoechoic cleft area between the 2 echogenic lines of the sacrum and iliac bone. With the transducer in the transverse position, the cleft was traced caudally to the end of the echogenic line representing the iliac bone. The posterosuperior part is fibrous while the antero inferior part is synovial. The cartilage lined portion extends more superiorly along the anterior aspect of the joint.

For each SI joint, the area with the highest number of CDUS flow signals was counted for statistical analysis. We did not use the mean calculation of color flow signals, but the scan with the highest number of CDUS flow signals.

In addition, enthesopathy was scored by grey scale as: hypoechogenicity/thickness: 0 to 1, calcifications/enthesophytes: 0 to 1, erosions: 0 to 1 and retrocalcaneal bursitis indicated by effusion: 0 to 1 scores 0 = absence 1 = presence. Power Doppler signal

Table 1. Descriptive and clinical data of AS patients

Descriptive Item	Number of Patients	minimum	maximum	Mean±SD
Peripheral Arthritis	20	2	8	4.9 ±1.889
No enthesis	20	6	15	8.85 ± 2.5603
Chest Expansion	20	1	4	2.1 ± 1.0563
BASMI	20	2.5	8	5.8 ±1.5424
BADAI	20	4.6	5.7	7.225± 1.2191
BASRI-Total	20	2	9	6 ± 1.8353
Knee GSUS	20	4	10	6.7±1.9762
PF thickness	20	1.35	2.93	2.247 ±0.3798
TA Thickness	20	1.91	2.97	2.369
ESR	20	15	65	35.95± 15.922
CRP	20	12	75	30.85± 20.391
ASDAS- CRP	20	3.5	5.7	4.205± 0.620

GSUS: grey US score, BASMI: The Bath Ankylosing Spondylitis Metrology Index, BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index, BASRI: The Bath Ankylosing Spondylitis Radiology Index, ASDAS: AS disease activity score, PF: plantar fascia, TA: tendoachillis

indicating vascularity at any of the four mentioned sites of enthesis, scored from (0 to 3). If Achilles tendon thickness ≥ 5.29 mm, or Plantar fascia thickness ≥ 4.4mm, so considered abnormal (D'Agostino, 2009).

No summation for a total score per patient was calculated as we scanned 4 axial and 2 peripheral joints as well as 4 sites of enthesopathy for (tendon, bursa, enthesis) by both GSUS and PDUS, so to avoid big scores, we preferred to estimate each item per se and study the change in it post treatment. All patients were assigned to treatment with S.C injection of either Etanercept 50 mg once weekly or Adalimumab 40 mg once biweekly or I.V infusion of Infliximab 3mg/kg at 0, 2 weeks, 6 weeks then every 8 weeks after screening test for T.B and HCV and HBV. All patients were enrolled in a follow up protocol (clinical examination, ESR, liver and kidney function tests) after first 4 weeks then every 2 months, till the end of the study at 6 months. The follow-up US examinations were performed 6 months after starting TNF antagonist therapy by the same investigators using the same US machine, same setting parameters and scanning technique as the previous one. The primary outcome measures were absolute change in disease activity measures and MSK US findings from baseline and after 6 months of anti TNFα therapy. The final measurement assessed the proportion of patients who achieved at least 50% improvement in BASDAI (BASDAI 50%) 6 months post treatment and similarly the proportion of patients who achieved at least ∆ ASDAS CRP ≥ 1.1after 6 months of treatment. The secondary outcome measures were to find the strong predictors for good response to anti TNF α therapy.

Statistical methods

IBM SPSS statistics (V. 23.0, IBM Corp., USA, 2015) was used for data analysis. Data were expressed as mean and SD for quantitative non-parametric measures in addition to both number and percentage for categorized data.

The following tests were done:

1. Comparison between 2 dependent groups for parametric data using Paired- t -test.
2. Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test.
3. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.
4. Ranked Spearman correlation test to study the possible association between each two variables among each group for non-parametric data
5. Logistics Multi-Regression analysis was used to search for a panel (independent parameters) that can predict the dependent variable parameter.

The probability of error at 0.05 was considered significant., while at 0.01 and 0.001 are highly sig.

RESULTS

This study included 20 patients with AS, (18 males and 2 females), who attended PMR department, Ain Shams University hospitals. Their mean age was 34.3± 9.5261, range (19-50) years and their mean disease duration was 9.65 ±4.3682, range (5-20) years. Twelve patients (60%) had extra articular manifestations in the form of psoriasis (3/12), conjunctivitis/uveitis (5/12), GIT symptoms (2/12).

All patients received anti TNFα therapy (11 Pts on Etanercept, 4 Pts on Adalimumab and 5 Pts on Infliximab), as well as NSAIDS. For DMARDS, 8 pts were receiving methotrexate, and 5 pts were receiving Salazopyrine.

Descriptive and clinical baseline data of the patients were expressed in table 1 above

All patients had clinical axial AS (14 pts with sacroiliitis,14 with spondylitis, 12 with hip arthritis) and 15 with peripheral arthritis.

The range of BASRI total was from 2 to 9 units with mean of 6 ± 1.8353. BASR- CS revealed that 9 patients

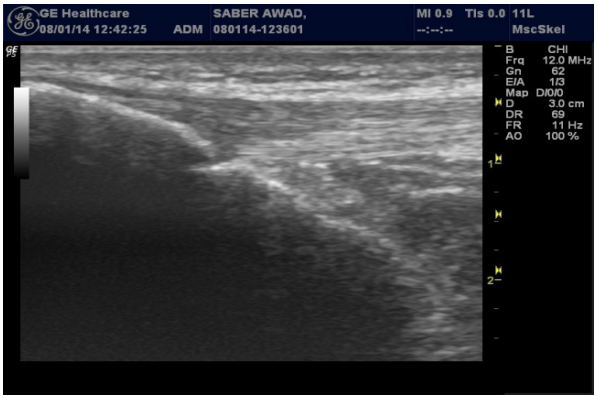


Figure 1. Pt N0 10: GSUS of Patellar tendon of RT knee. . Erosion in tibial tuberosity at insertion of PT

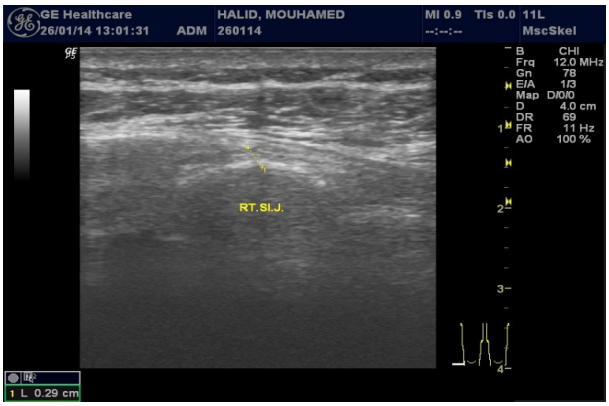


Figure 2. Pt N05: Sonography of sacroiliac joint longitudinal view. GSUS of RT S.I joint with altered echogenicity and synovial

had score (1), 9 patients had score (2) and 1 patient had score (3) while one patient had normal cervical joints. On the other hand BASRI- LS showed that 4 patients had score(1),10 patients had score (2), five patients had score (3) while 1 patient had normal lumbar joints. Similarly, BASRI- SI showed that 7 patients had score (2), 10 patients had score (3), while 3 patient had score (4).

All patients underwent MSK US scanning of axial and peripheral joints (hip, S.I and knees) and four sites of enthesis. At hip joints, GSUS showed evidence of synovitis (effusion, hypertrophy and altered echogenicity) was present in 19 patients: 7 patients (G1), 11 patients (G2) and 1 patient (G3), while bursitis was recorded in 11 patients (55.5%) and 7 patients (35%) had erosions at greater trochanter of the femur as well as vascularity signals of synovium registered by PD scanning was found in 10 patients (G1) and 7 patients (G2).

For the knee joints GSUS showed: altered echogenicity in patellar tendon (PT) in all patients, osteophytes were recorded in 10 patients while erosions at site of PT insertion were found in 8 patients (Figure 1). Knee synovitis was found in 12 patients (G2) and 8 patients (G3) with mean grey scale score 6.7/12 ±1.976. Knee PDUS scanning showed vascularity signals in all patients: 4 patients (G1), 15 patients (G2) and 1 patient (G3). while mean PDUS score was 8.6 /15± 1.76.

Sacroiliac joints scanning: altered echogenicity as evidence of synovitis in 17 patients, while 3 patients had no evidence of synovitis (Figure 2). Ankylosed joints were recorded in 3 patients. This was confirmed by PDUS/ CDUS scanning: 7 patients had (G1) vascularity signals while 2 patients had (G 2) and 1 patient had (G3), while 3 patients had no signals.

Regarding sites of enthesis, all signs of enthesopathy were registered by GSUS and PD: At ankle, calcifications in TA, altered echogenicity and thickening were present in plantar fascia (PF) and tendo Achilis of all patients (100%), the mean thickness of PF recorded was 2.247± 0.37985 cm. While the mean thickness of TA was 2.369± 0.31119 cm. Swollen retrocalcaneal bursa was reported in 13 patients with positive PD signals in 9 patients (G1) and 11 patients (G2). Figure 3

The primary outcomes

All patients received regular doses according to anti TNF α type for six months then clinical and radiological re-assessments were done. All patients were improved regarding clinical, laboratory, radiological and MSK scanning. Comparison between patients mean data pre and post treatment by student “t”test is expressed in table 2.

Regarding qualitative data: extra articular manifestations, radiological and other MSK US findings, statistical differences by Chi square were illustrated in table 3 below.

All patients had average range of CBC, liver and kidney functions without any significant abnormalities after treatment.

At 6 months post treatment, 7 patients had ASDAS CRP ≥ 1.3 < 2.3 with a mean value of 2.15± 0.815 (high disease activity), with reduction (difference) value -1.555 ± 0.526 which indicates patient improvement according to ASAS, while 4 patients had BASDAI score < 4 with a post treatment mean value of 4.745±1.3133 which still indicate active disease. Similarly in US scanning, mean plantar fascia thickness became 1.7455 ±0.4628 and TA thickness became 1.7655 ± 0.33594 cm which reflect enthesopathy though patients improvement with a significant difference in PF and TA thickness (t= 6.948, p=0, t = 8.076, p=0) respectively (Figure 4).

From Table 3, it is obvious that no significant change in plain radiography of cervical, lumbar and both S.I joints, while a significant change (decrease) in synovitis, enthesopathy and power Doppler signals of vascularity

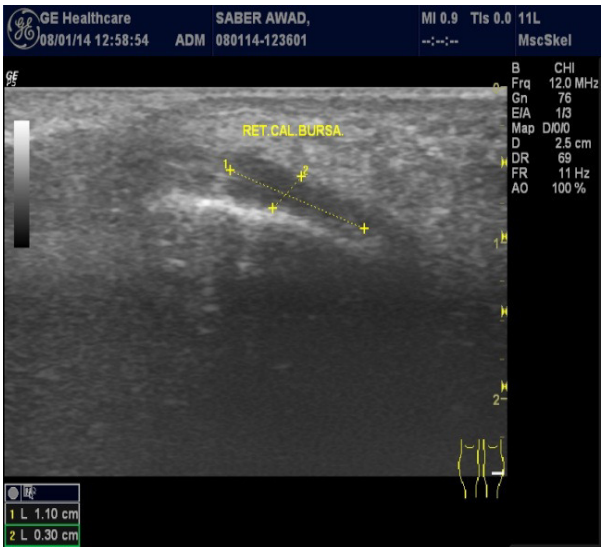


Figure 3. Pt N0 7: GSUS scanning at RT ankle (enthesis) Swollen retrocalcaneal bursa at RT ankle

of all scanned areas, as well as extra articular manifestations.

To elaborate the effectiveness and clinical response of anti TNF α therapy ,we classified patients after therapy into BASDAI 50% responders and non responders BASDAI 50% response is defined as a 50% improvement of the initial BASDAI (BASDAI 50): we noticed that 17 patients achieved BASDAI 50% as their median and (25-75) percentiles was 7 (6.5) before therapy and became 3.5 (1.2) and there was no significant difference in most of clinical, laboratory and radiological data between responders and non responders except for the change of (∆) BASDAI (Z= 2.711, P< 0.01), ∆ ASDAS CRP (Z= -2.12, P = 0.034), ∆ of ESR (Z= 1.964, P= 0.05) and ∆ chest expansion (Z= -1.997, p =0.046), while when classifying the patients according to ASDAS CRP ≥ 1.1 into patients with clinically important improvement and patients without, we found that16 patients achieved clinically important improvement as their median and (25-75) percentiles was 3.95 (3.8 - 4.725) before therapy then became 2.1 (1.9 - 3.2) and the difference was statistically significant (Z =-2.94, P=0.003). On comparing all patients variables between improved and non improved groups, we noticed a significant difference in (∆) BASMI (Z= -1.987, P = 0.047), (∆) chest expansion (Z= -2.031, P = 0.047), (∆) CRP (Z= -2.94. P=0.003), (∆) ESR (Z= -2.275, P <0.05), ∆ hip synovitis (P<0.05), (∆) knee PD (P<0.05), (∆) sacroiliac PD (P<0.05), (∆)sacroiliac synovitis (P<0.05), and (∆) plantar fascia thickness (Z= -1.987, P=0.047).

All patients (5/5) who received Etanercept achieved clinical important improvement as well as 82% and of pts on infliximab (9/11), while only 50% of pts (2/4) on Adalimumab did. But no significant differences were found between the percentage of BASDAI 50% responders versus non responders between the three TNF-α blocking agents at six months (*P* = 0.640), and the same was found according to ∆ ASDAS CRP improved vs non improved pts (P = 0.172).

Table 2. Comparison between clinical and radiological data of AS patients pre and post treatment

Variables	T	p	S
No enthesis	8.722	0.01	HS
Chest Expansion	-4.426	0.01	HS
BASMI	3.911	0.001	HS
BADAI	9.234	0.01	HS
BASRI-Total	-0.329	0.615	NS
ESR	9.416	0.0.01	HS
CRP	5.076	0	HS
ASDAS-CRP	12.356	0	HS
Total knee GSUS	10.258	0	HS
TA thickness	8.076	0	HS
PF thickness	6.948	0	HS

TA: tendo achillis, PF: plantar fascia, GSUS :grey scale US
This table revealed high significant decrease in ASDAS CRP, BASDAI,BASMI, ESR, CRP as well as number of enthesis

Relation of BASDAI 50% to ASDAS CRP

A significant positive correlation between BASDAI 50% and both baseline and post treatment ASDAS CRP (r=0.657, P <0.05, 0.505, P <0.05) respectively.

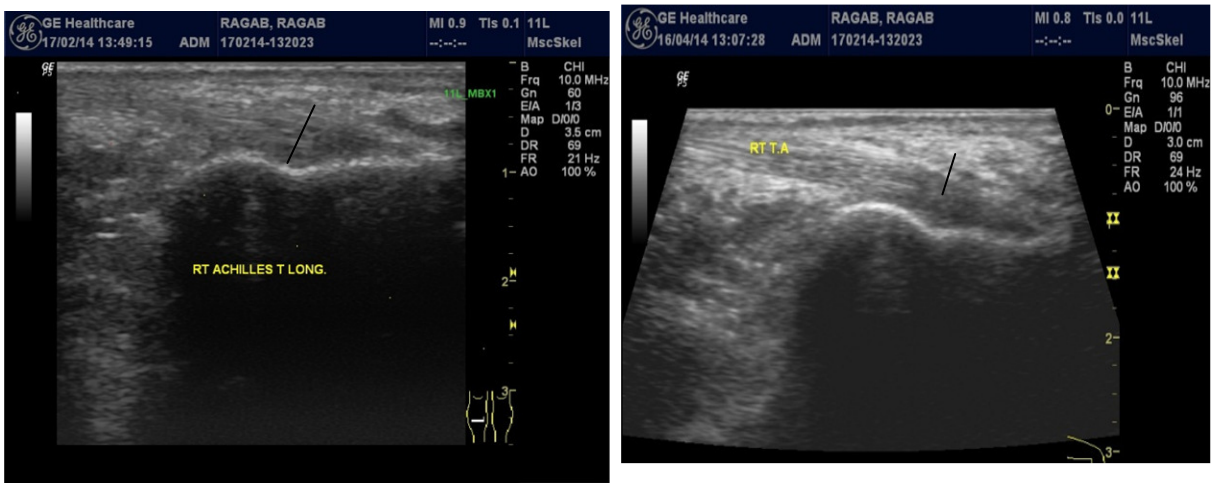
Table 3. Comparison of Pre and Post treatment values of patients qualitative data.

Variables	Pearson Chi	P	Sig
EAM	6.667	.010	S
Hip synovitis	5.227	.022	S
Hip bursitis	15.667	.001	S
Hip PD	21.800	.000	HS
GT enthesopathy	6.465	.011	S
S.I synovitis	5.865	.053	S
S.I CDUS	11.250	.004	S
Knee Synovitis	24.000	.000	HS
Knee PDUS	26.650	.000	HS
PT enthesopathy	10.000	.002	HS
TA PD	21.053	.000	S
Retrocalc. Bursitis	0.921	.337	NS
PF enthesopathy	10.000	.002	HS
BASRI Lumbar	2.667	.615	NS
BASRI CX	6.624	.085	NS
BASRI S.I	2.103	.349	NS

EAM: extra articular manifestations. JSN: joint space narrowing, CDUS: color Doppler US
This table showed a significant difference in EAM, GSUS and PDUS synovitis of hip, S.I and knee joints and tenosynovitis as well as enthesopathy

Before Therapy

After Therapy



A: GSUS of AT showed increased thickness

B: GSUS of same pt. showed reduced thickness of AT

Figure 4. Patient N0 12 : GSUS of RT TA before and after therapy

Correlation of (∆) ASDAS CRP ≤1.1 with baseline clinical parameters

It was found that median clinical important improvement (∆ ASDAS ≥1.1) was significantly correlated with age, baseline clinical and sonographic patients characteristics (Table 4).

The secondary outcomes

To search for predictors that can predict the major clinical response BASDAI 50%, factors associated with achieving BASDAI 50% were modeled using linear regression analysis. Covariates included: disease duration, baseline BASDAI, high ESR > 25mm/hr, high CRP > 20mg/L,

Table 4. Correlation between Δ ASDAS ≥1.1 and clinical and US findings of AS patients

	Δ ASDAS ≥1.1		
Variables	**r**	**P**	**Sig**
Age	0.544	0.022	S
Periph. Arthritis B	0.453	0.046	S
ASDAS CRP B	0.657	0.002	HS
ESR B	0.504	0.024	S
No of Enthesis B	0.811	0.00	HS
BASMI B	0.565	0.042	S
BASDAI B	0.753	0.001	HS
Hip synovitis B	0.801	0.00	HS
S.I synovitis B	0.5013	0.022	S
BASRI total B	0.689	0.007	HS

B: baseline
This table showed that Δ ASDAS ≥1.1 was significantly correlated with baseline peripheral arthritis, number of enthesis, BASMI, ASDAS CRP, BASDAI, ESR, hip synovitis , S.I synovitis and BASRI total

Table 5. 3rd model of a logistic stepwise multi-regression analysis for predictors of BASDAI 50%

	Reg.	T	p	Sig.			
Model 3	**Coef.**				**F- ratio**	**p**	**Sig**
Constant	1.345	5.154	0	HS			
High ESR B	0.01	1.909	0.073	NS	4.817	0.022	S
No enthesis	- 0.095	- 3.046	0.007	HS			

This table showed that : baseline high ESR and No of enthesis are best predictors for major

peripheral arthritis, number of enthesis, BASRI Cx, BASRI lumb., enthesopathy by US, PF thickness > 4mm by US, PD vascularity signals in S.I joints and a logistic stepwise multi-regression analysis in 3 models revealed that baseline ESR and number of enthesis were the most sensitive predictors for BASDAI 50% (Table 5) (only model 3 is showed).

On the other hand, to find the most sensitive predictors for clinical important improvement (Δ ASDAS CRP ≥ 1.1), a stepwise multi linear regression analysis was done and same covariates for BASDAI 50% were used and showed that increase number of peripheral arthritis, high basal ASDAS (>2.1) and PF thickness > 4.4 mm were the most sensitive predictors for good response to treatment.

DISCUSSION

This study evaluated the value of MSK US scanning of axial (sacroiliac, hip) and peripheral (knee) joints as well as enthesopathy in four sites, before and six months after anti TNFα therapy in AS patients. Also, this study addressed the assessment of clinical response to anti TNF α therapy and to detect the best prognostic predictors of good response to treatment. All patients had evidence of axial involvement and with peripheral arthritis in 15 patients. All were eligible to anti TNFα therapy according to ASAS/EULAR recommendations (Braun et al., 2011) as mean BASDAI was7.225± 1.2191 reflecting active disease, and they gave history of failed treatment with two DMARDS and NSAIDs. We used two disease activity indices (BASDAI- ASDAS CRP) for choosing patients legible to anti TNFα therapy in order not to miss any patient who will benefit from therapy As It was mentioned recently, that using BASDAI as the only criterion to decide anti-TNF treatment could exclude many patients to be treated with anti-TNF therapy although they had disease characteristics (high CRP, AGE < 40 years, HLAB27), that are associated with good outcomes (Vastesaeger et al., 2014). All patients had high disease activity as mean ASDAS CRP was 4.205± 0.620, with extra articular manifestations and limited chest expansion mean (2.1 ± 1.056)cm, and high score of BASMI up to 8 units. All patients had radiological changes as recorded in BASRI total especially in lumbar

and sacroiliac joints section. Six month of regular treatment by anti TNFα drugs resulted in significant clinical and laboratory improvement marked reduction in disease activity indices. The results are in agreement with the results from RCTs, indicating that anti-TNFα therapy is an effective treatment option for patients with AS (Lord et al., 2010). According to EULAR 2015, MSK US was not recommended of neither diagnosing or monitoring disease activity of axial SpA, while recommended in detection of peripheral arthritis and enthesitis and monitoring disease activity particularly synovitis and enthesitis in peripheral SpA (Mandl,2014). MRI is, through its ability to detect inflammatory changes in bone and soft tissues, the most sensitive imaging modality for recognizing early spine and sacroiliac joint changes in AS. However, MRI is also limited in patients with metal implants or pacemakers, or with claustrophobia (Inanc et al.,2005). Although in literature, MSK US was allowed for assessment of peripheral involvement in SpA, we tried in the current study, MSK US in the assessment of axial and peripheral involvement and monitoring short term effect of anti TNFα therapy. We assessed synovitis of hip, S.I and knee joints by grey scale and power Doppler US. We assumed that by GSUS any change in echogenicity, irregularities, tenosynovitis in ligaments attachment and erosions in joint line in sacroiliac joints are evidence of synovitis, as well as PDUS signals in lower third (antero inferior) part of the joint. Diagnosing of Sacroiliitis by GSUS in 17 patients (85%), while only 14 pts had clinical sacroiliitis before treatment however, by PDUS and CDUS we recorded flow signals in 50% of patients. Six months after treatment, the blood flow signals in the sacroiliac joints were unremarkable and recorded only in 10% of patients. This was in agreement with a recent study as authors used PDUS for evaluation of infliximab treatment for sacroiliitis in pts with AS, they just recorded blood flow signals inside the joints as evidence of synovitis, which significantly decreased post treatment (jiang et al., 2013). On the other hand, we scored active sacroiliitis by CDUS (0-3) in 50% of patients in the form of 7pts (G1), 2pts (G2) and 1pt (G3) before treatment, which was in agreement with Klauser et al. (2005), who recorded active synovitis only in 19% of his patients by unenhanced CDUS. The current study implied SOLAR score which is a very suitable instrument for the qualitative and quantitative evaluation of large joint involvement in AS patients and allows for treatment monitoring (Schafer et al., 2013). We scanned both hips as another axial joints but a 0-3 score was used for GSUS and PDUS according to SOLAR and we scored hip synovitis in 19 pts with 11 pts were (G2) by GSUS and confirmed by PDUS prior to treatment then recorded in 12 pts with high significant difference (P< 0.001). This was in accordance with Schafer et al. (2013), they reported a significant difference 6 months post treatment in hip synovitis by GSUS. In addition, scanning of knee joints was done with a score 0-12 according to SOLAR score. The mean score of GSUS knee was 6.7±1.9762 before therapy and was reduced to 3.1 ±1.338 with significant difference (P<0.01), and also a significant improvement in PDUS (p <0.001) which was similar to previous study by Schafer et al. they reported a knee GSUS mean score of 5.3 ± 2.9 at baseline and was reduced six months after therapy to 2.8 ± 2.8 (P< 0.01).

Regarding enthesopathy all patients showed sonographic evidence of enthesopathy by GSUS with increased thickness at plantar fascia and tendoAchillis at the start of the study and interestingly, anti TNF α therapy effectively reduced enthesopathy at PF, and TA with significant difference (t= 6.947, P<0.001,t= 8.076, P< 0.001) respectively. This was comparable to previous studies with anti TNF α therapy trials in SpA (Aydin et al., 2009). Many previous studies estimated the value of MSK US in diagnosing enthesopathy in SpA. After D'Agostino (2002), Grey-scale enthesitis was mostly characterized by the loss of normal fibrillar echogenicity of the tendon insertion (83%) with or without an increase in tendon thickness and periosteal changes (erosions or new bone formation), however these structural damage still less representative of enthesopathy. A recent study by Hassan et al., reported that both grey scale and power Doppler US in evaluation of enthesopathy, effectively help in diagnosing peripheral SpA.

Grey-scale enthesitis was characterized by increasing thickness (94% of studies), hypo echogenicity (83%), enthesophytes (69%), erosions (67%), calcifications (52%), associated bursitis (46%) and cortical irregularities (29%) (Gandjbakhch et al. 2011).

Initially, when analysis the signs of enthesopathy, 75% of patients had altered echogenicity in greater trochanter ligaments, with evidence of erosions in 35 %, while altered echogenicity in Patellar tendons in all pts with 40% had erosions and 40 % had osteophytes. Approximately 50-55% of our patients had initial Power Doppler signals in bursal enlargement and other enthesis sites (PT- GT) and within this group there was a response rate of 70% in PD scores after therapy. Accordingly, these findings were similar to those of previous studies (Aydin et al., 2009). We can conclude that both GSUS and PDUS are Valuable tools for diagnosis and monitoring response to treatment of enthesopathy in AS. Within the area of SpA, Power Doppler ultrasonography is currently being used to detect enthesitis and to assess response of enthesitis to therapy (Kiris et al., 2006).

After power Doppler was applied to the technique for evaluating active inflammation in tendons insertion and related bursae, more studies highlighted the specificity of vascular signals in diagnosing SpA enthesitis (D'Agostino et al., 2011; de Miguel, 2009; de Miguel, 2011; Feydy et al., 2012).

To evaluate a definite response to anti TNF α therapy on measurement of disease activity (clinical and

laboratory) and MSK US inflammatory findings, we classified the patients two times: one according to BASDAI 50% into responders and non responders subgroups and second time according to ∆ ASDAS CRP ≤1.1 into clinically improved and non clinically improved subgroups. We found that at six months post treatment, thirteen pts achieved BASDAI 50%, while 16 patients achieved clinical improvement with a significant difference in most of measurements of disease activity, and MSK US inflammatory findings (P <0.05). This elucidate that ∆ ASDAS CRP ≤1 was a reliable and sensitive index of good response of anti TNF α therapy and the use of selection disease activity instrument improves the outcome of therapy in the selected populations.

This was previously concluded by Vastesaeger et al. (2014), that replacing the disease activity measure in anti-TNFα treatment recommendations from BASDAI to ASDAS may lead to better outcomes of therapy. Moreover, we noticed that 100% of pts (5/5) who received Etanercept, achieved clinical improvement and same for 82% of pts (9/11) who received Infliximab, while 50% of Pts (2/4) on Adalimumab achieved clinical improvement. This could be explained by the wide range of disease duration (5-20 ys) as all pts who were on Etanercept and Infliximab had shorter disease duration (5-10 ys) than those on Adalimumab (15-20 ys) in this cohort, and also may be due to that most of the pts (55%) were on Etanercept, however a larger sample of patients was needed for accurate comparison.

In a previous study by Lord et al. (2010), authors evaluated effect of 3 anti TNF α drugs in 261 AS patients, they reported that higher percentage of pts who received Etanercept achieved major clinical response BASDAI 50%, followed by Infliximab then Adalimumab.

However, no significant difference was found between the three anti TNF α drugs on BASDAI 50% responders vs non responders or between ASDAS CRP improved vs non improved (p >0.05), this was in accordance with Rudwaleit et al. (2004).

In addition we recorded a positive correlation between BASDAI 50% and both baseline and post treatment ASDAS CRP which indicates a strong association between the two disease activity measures when used to monitor response to treatment.

Moreover, the mean of ASDAS CRP after treatment was strongly correlated with age, baseline peripheral arthritis, number of enthesis, BASMI , ESR, BASDAI A and BASRI total (p = 0.015, P =0.005, P= 0.001, P= 0.042, P= 0.017, P = 0.001 and P= 0.009) respectively as well as with baseline MSK US inflammatory findings, as S.I synovitis and S.I irregularities (P =0.22, P = 0.26) respectively.

Our aim was to find sensitive predictors that can predict good response to anti TNF α therapy so the major clinical response BASDAI 50%, was tried and factors associated with such response were modeled using stepwise linear regression analysis in 3 models revealed that baseline high ESR and number of enthesis were the most sensitive predictors for BASDAI 50% which is comparable to previous study by Rudwaleit et al. (2004) who reported that acute phase reactants (ESR,CRP) were significantly associated with response to treatment.

Similarly, ∆ ASDAS CRP was tried and same covariates were used to find best predictors of good response and stepwise linear regression curve showed that presence of peripheral arthritis, high basal ASDAS (>2.1) and PF thickness > 4.4 mm were the most sensitive Predictors.

CONCLUSION

The present study has demonstrated that ultrasound is considered a promising tool for assessing axial and peripheral arthritis and enthesopathy in AS patients and effectively help in monitoring short term effect of anti TNFα therapy. Studies on a larger number of patients should be performed in the future to better confirm our exploratory findings.

AUTHORS CONTRIBUTIONS

Saber Z.N. made substantial contributions to conception and design and acquisition of MSK US scanning , and have been involved in drafting the manuscript and revising it critically for important intellectual content. Younis BT. .. contributed to the analysis and interpretation of data Ibrahim Y. made contributions to design and analysis of X-rays findings and revising the final manuscript.

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