Colour Doppler ultrasonography can be used to detect the changes of sacroiliitis and peripheral enthesitis in patients with ankylosing spondylitis during adalimumab treatment

Z. Hu, M. Xu, Q. Wang, J. Qi, Q. Lv, J. Gu

Department of Rheumatology, the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China.

Abstract

Objective

To investigate whether colour Doppler ultrasonography (CDUS) can be used to detect the effect of adalimumab on sacroiliitis and peripheral enthesitis in patients with ankylosing spondylitis (AS).

Methods

AS patients (n=41) received 40 mg adalimumab every other week for 24 weeks. BASDAI, BASFI, CRP, MRI examinations of the sacroiliac joints (SIJs) and CDUS examinations of both SIJs and 10 peripheral entheseal sites were taken at baseline, week 12, and week 24. We scored the MR images by SPARCC method, recorded the resistive index (RI) value of SIJs and graded the blood signal on a semi quantitative 0–3 scale. We also scored lesions of peripheral entheses seen by CDUS. We analysed the associations between the results of CDUS and clinical indices and MRI data.

Results

Significant reduction in mean CDUS score of SIJs and peripheral enthesitis and increase in mean RI value were observed in AS patients treated with adalimumab for 12 weeks and 24 weeks as compared with baseline (all $p<0.05$). The CDUS scores of SIJs and peripheral enthesitis positively related with clinical assessments (including BASDAI, BASFI, and CRP), while the RI value negatively related with them at all visits (all $p<0.05$). The results of CDUS also correlated well with the MRI data (all $p<0.05$) during adalimumab treatment in AS patients.

Conclusion

Our study found that CDUS could be used to detect the changes of sacroiliitis and peripheral enthesitis in AS patients under adalimumab therapy.

Key words

ankylosing spondylitis, ultrasonography, tumour necrosis factor inhibitors

Zaiying Hu, MD, PhD
Manlong Xu, MD, PhD
Qiaoyuan Wang, MS
Jun Qi, MD, PhD
Qing Lv, MD, PhD
Jieruo Gu, MD, PhD

Please address correspondence and reprint requests to:
Dr Jieruo Gu,
600 Tianhe Road,
Department of Rheumatology,
Third Affiliated Hospital of
Sun Yat-Sen University,
Guangzhou 510630, China.
E-mail: gujieruo@163.com

Received on February 13, 2015; accepted in revised form on May 28, 2015.

Funding: this study was supported by the Medical Scientific Research Foundation of Guangdong Province (B2014142), the National Natural Science Foundation of China (81373181) and 5010 Subject of Sun Yat-sen University (2007023).

Competing interests: none declared.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterised by enthesitis and primarily involves the axial skeleton (1). Sacroiliitis is one of the earliest manifestations of AS, which is diagnosed by clinical findings (for example: inflammatory low back pain) and imaging (2-4). Peripheral enthesitis is another characteristic feature of AS and may involve synovial tissue and entheses (5). X-ray and magnetic resonance imaging (MRI) are frequently used as image tools to investigate sacroiliitis and peripheral enthesitis in AS patients. X-ray could show the structural lesion of sacroiliac joints (SIJs) and severe or longstanding peripheral enthesopathy, but could not show the lesions in the early stage of disease. MRI can quantify active inflammatory lesions of SIJs and entheses (6-8). However, MRI is relatively expensive and time-consuming, and its routine use in patient visits during therapy would be difficult. Ultrasonography (US) is an inexpensive, non-invasive and non-radiating technique, which can be used in daily clinical practice (9, 10). It has been demonstrated that signs of active sacroiliitis can be detected by colour Doppler US (CDUS) in AS patients (11, 12). Some studies have also proved the reliability of CDUS to evaluate peripheral enthesitis in patients with AS (13, 14). Although it has been suggested that US might be superior to MRI in detecting early signs of enthesopathy in spondyloarthropathy (SpA), evidences are still poor (15).

Treatment options to AS are limited and mainly consist of non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy (16). Efficacy of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate is uncertain to AS (17). Tumour necrosis factor α (TNF-α)-blocking agents have been shown to be highly effective in treating AS patients especially in whom are resistant to NSAID therapy (18-20). Adalimumab, a recombinant, full-length immunoglobulin, is an anti-TNF-α monoclonal antibody containing exclusively human sequences with a high affinity for human TNF and is typically administered subcutaneously every other week. Adalimumab has shown great efficacy and favorable safety in clinical trials in AS patients (21-26). The effect of adalimumab is usually demonstrated by clinical assessments and/or MRI. Great part of previous studies in SpA has been conducted just on peripheral articular sites despite using of different ultrasonography tequiniches (27-30). Whether CDUS can monitor the changes of sacroiliitis and peripheral enthesitis in AS patients under adalimumab treatment has not yet been estimated.

In the present study, we aimed to investigate whether CDUS can be used to detect the effect of adalimumab on reducing inflammation in SIJs and peripheral entheses in patients with AS.

Materials and methods

Patients

Patients were adults (≥18 and ≤65 years old) diagnosed as AS defined by the modified New York criteria (31), who had been treated unsuccessfully (nonresponsive or lack of tolerance) with ≥1 NSAIDs. Patients included at baseline also fulfilled at least 2 of the following 3 criteria: a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (32) score ≥4, total back pain visual analogue scale score ≥40, or morning stiffness of ≥1 hour in duration. All patients were recruited consecutively from the department of rheumatology, the Third Affiliated Hospital of Sun Yat-sen University from 2010 to 2013.

The study was approved by the local ethics committee and was performed in accordance with the ethics principles of the Declaration of Helsinki. Written informed consent was obtained from each patient before any study-related procedure occurred.

Study design

All patients (n=41) received 40 mg adalimumab every other week for 24 weeks. Study visits occurred at baseline, week 12, and week 24. Patients' BASDAI, Bath Ankylosing Spondylitis Function Index (BASFI) (33), and C-reactive protein (CRP) were measured at every visit. The examinations of CDUS on SIJs and peripheral entheses and MRI on SIJs were also performed at all visits.

Ultrasonography examination

CDUS examinations were performed by an ultrasonographer (QY Wang, 5 years of experience in musculoskeletal ultrasound) who was blinded to the treatment of patients and unknown of the study design when performing the examinations. We used a 5–12 MHz linear array transducer to detect sacroiliitis and peripheral enthesitis (Aloka α5, Tokyo, Japan). The processing settings (*i.e.* transducer orientation, positioning of the probe and enthesis, adherence to standard planes, machine settings, and room temperature) remained constant throughout all sessions.

• *Sacroiliitis*

Patients were examined in the prone position. The probe in the transverse position was put to the back of the sacral bone and the sound beam was inclined a little downside to detect the site of SIJs. The probe was then set obliquely and slightly anticlockwise to detect the left SIJ and clockwise to detect the right SIJ (12). Blood flow inside or around the SIJs were examined by CDUS (examples shown in Fig. 1). The corresponding resistive index (RI) value was recorded. Measurements of RI were repeated 3 times, and the mean value was used for analysis. We also graded the Doppler blood signal of SIJs on a semi quantitative scale (range 0–3; 0 = no signal, 1 = single vessel signal, 2 = punctate vessel signals, 3 = confluent vessel signals) (34). The CDUS scores of SIJs were recorded.

• *Peripheral enthesitis*

Patients lay in a supine position with knees flexed to 60° to explore the quadriceps tendon insertion, the superior patellar tendon insertion, and the inferior patellar tendon insertion at the anterior tibial tuberosity. The insertion of Achilles tendon and the plantar aponeurosis insertions at the calcaneous were examined with patients placed in a prone position with ankles at neutral flexion. All entheseal areas were scanned bilaterally. The method to score peripheral enthesitis was described in previous reports (35-37). Enthesis thickness, structure, calcification/bone proliferation, erosion, bursa and colour Doppler signal in the quadriceps tendon, superior and inferior patellar tendon, Achilles tendon, and proximal plantar fascia were scored (examples shown in Fig. 2). All lesions were scored in a dichotomous manner (present or absent). It was a weighted score previously calculated by logistic regression that overestimates the score of three elemental lesions: calcification (0 = absent or 3 = present), Doppler (0 or 3) and erosion (0 or 3), while scoring tendon structure, tendon thickness and bursa as either a 0 (absent) or 1 (present) (37). As bursitis was not de-

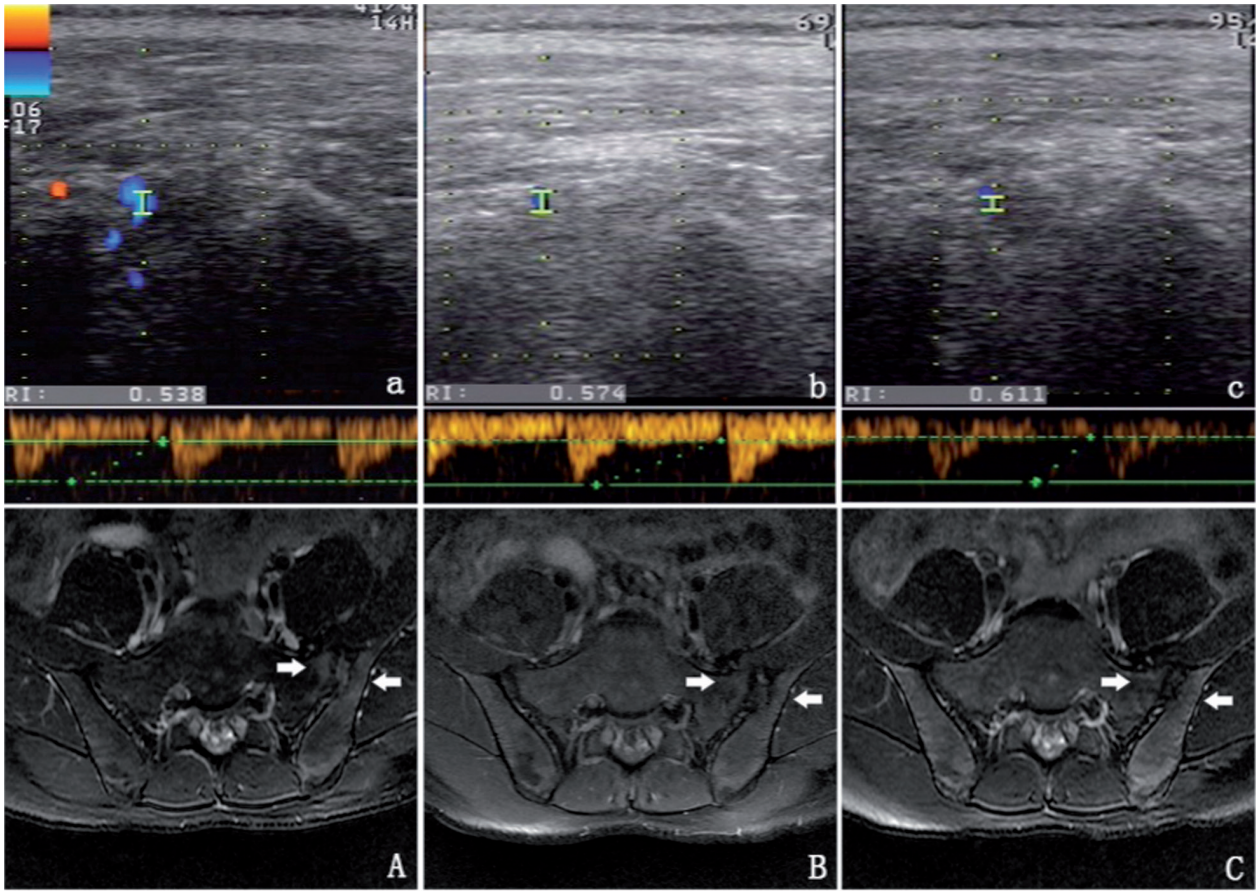

Fig. 1. A male patient with ankylosing spondylitis had left side sacroiliitis (grade 3) with low resistive index (RI) value at baseline (a). This sacroiliitis can also be seen on MRI (A, arrows); The Doppler signal reduced significantly (grade 1) after 12 weeks of adalimumab and the RI value increased (b). The MR images also showed decreased inflammation (B, arrows); The RI value continued to increase after 24 weeks of adalimumab (c) and the blood signal remained little (grade 1). The inflammation seen by MRI was further decreased (C, arrows).

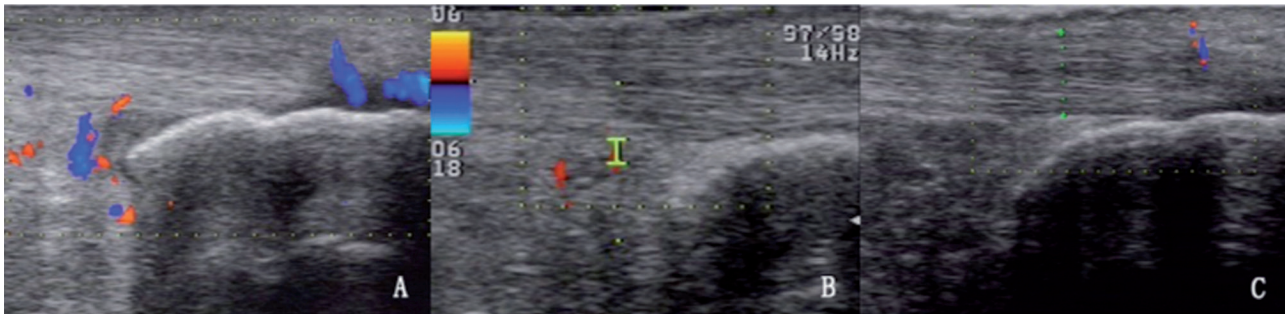

Fig. 2. Doppler signal and bursitis appeared in the left insertion of Achilles tendon in a male patient with ankylosing spondylitis at baseline (**A**). The bursitis disappeared and the Doppler signal reduced after 12 weeks of adalimumab (**B**), and the Doppler signal removed completely after 24 weeks of adalimumab (**C**).

tectable in superior patellar tendon and proximal plantar fascia due to the absence of bursa in these areas, the total CDUS score of peripheral enthesitis can range from 0 to 116.

MRI procedure

MR images of SIJs were performed using a 1.5T scanner (Signa Excite II; GE Medical Systems, Fairfield, CT, USA). T1 and short inversion time inversion recovery (STIR) sequences were investigated. After all MR examinations finished, images were scored in a random order by two independent readers (XHW, radiologist, over 20 years of experience in musculoskeletal imaging; and ZYH, rheumatologist, 8 years of experience). The mean of the two readers' scores was used for all analyses. The SPARCC scoring method was used to score the inflammatory lesions in SIJs (38). Total SIJ SPARCC scores can range from 0 to 72. Examples were shown in Figure 1. Details of this method are available online at www.arthritisdoctor.ca.

Statistical analysis

Variables were tested for normality by applying the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) and *t*-test were used to compare the means. Correlations between the results of CDUS and clinical assessments and MRI data were analysed by Pearson's or Spearman's test, as appropriate. *P*-values <0.05 (2-tailed) were considered significant. All statistical analyses were carried out in SPSS v.15.0.

Results

Characteristics of study subjects

In this study, 38 patients were men, and the other 3 were women. Mean age was 27.7 (range 18-47) years and average age at diagnosis was 20.5 (range 14-40), with a mean duration of disease of 7.2 (range 1-20) years. 39 of them were HLA-B27 positive, and 2 were HLA-B27 negative.

Improvement of clinical assessments

The mean ± SD scores of BASDAI, BASFI and CRP in AS patients were shown in Table I. After 12 weeks of adalimumab treatment, AS patients got significant reduction in BASDAI, BASFI and CRP values (all $p<0.01$). At week 24, the value of BASDAI, BASFI and CRP also drop significantly as compared with baseline (all $p<0.01$). P values were listed in Table II.

Changes of CDUS scores

And peripheral enthesitis and the RI value of SIJs were shown in Table I. The abnormalities of 410 examined entheseal sites of AS patients at baseline were shown in Table III. The mean CDUS score of SIJs and peripheral enthesitis decreased significantly from baseline to week 12, and from baseline to week 24 (all $p<0.05$). The mean RI

Table I. Clinical, CDUS and MRI data of AS patients during adalimumab therapy*.

	Baseline	Week 12	Week 24
BASDAI	4.9 ± 2.2	2.3 1.7	1.4 ± 1.5
BASFI	3.7 ± 2.2	1.9 ± 1.6	1.5 ± 1.8
CRP (mg/l)	22.1 ± 20.8	5.6 ± 12.5	2.8 ± 6.1
CDUS score of SIJs	1.33 ± 1.27	1.11 ± 1.19	1.08 ± 1.10
RI value of SIJs	0.55 ± 0.26	0.79 ± 0.26	0.81 ± 0.25
MRI score of SIJs	10.4 ± 9.5	4.7 ± 6.1	3.8 ± 5.3
CDUS score of PE	18.6 ± 9.2	16.7 ± 9.1	15.5 ± 10.9

*Values were mean ± SD. CDUS: colour Doppler ultrasonography; AS: Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; CRP: C-reactive protein; SIJs: Sacroiliac Joints; RI: Resistive Index; PE: peripheral enthesitis.

Table II. *P*-values of comparing clinical, CDUS and MRI data between baseline and week 12 and week 24 in AS patients during adalimumab treatment.

	Baseline *vs*. Week 12	Week 12 *vs*. Week 24	Baseline *vs*. Week 24
BASDAI	0.002	0.011	0.000
BASFI	0.003	0.047	0.001
CRP (mg/l)	0.000	0.004	0.000
SIJs CDUS score	0.038	0.039	0.024
SIJs RI value	0.021	0.347	0.016
SIJs MRI score	0.001	0.041	0.000
PE CDUS score	0.003	0.013	0.001

CDUS: colour Doppler ultrasonography; AS: Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; CRP: C-reactive protein; SIJs: Sacroiliac Joints; RI: Resistive Index; PE: peripheral enthesitis.

Table III. CDUS abnormalities of 410 examined peripheral entheseal sites of AS patients at baseline.

Abnormalities	Sites					
	Quadriceps tendon	Superior patellar tendon	Inferior patellar tendon	Achilles tendon	Plantar fascia	All sites
Calcification, n (%)	4 (4.9)	2 (2.4)	2 (2.4)	6 (7.3)	1 (1.2)	15 (3.7)
Doppler signal, n (%)	2 (2.4)	8 (9.8)	8 (9.8)	18 (22.0)	3 (3.7)	39 (9.5)
Erosion, n (%)	5 (6.1)	10 (12.2)	11 (13.4)	22 (26.8)	8 (9.8)	56 (13.7)
Tendon structure, n (%)	27 (32.9)	31 (37.8)	25 (30.5)	24 (29.3)	3 (3.7)	110 (26.8)
Tendon thickness, n (%)	27 (32.9)	28 (34.1)	27 (32.9)	20 (24.4)	2 (2.4)	104 (25.4)
Bursitis*, n (%)	5 (6.1)	*	8 (9.8)	8 (9.8)	*	21 (8.5)
At least one abnormality, n (%)	19 (46.3)	33 (80.5)	27 (65.9)	25 (61.0)	6 (14.6)	110 (53.7)

*Bursitis was not detectable in superior patellar tendon and proximal plantar fascia due to the absence of bursa in these areas. CDUS: colour Doppler ultrasonography; AS: Ankylosing Spondylitis; n: number of patients.

value of SIJs increased obviously after 12 weeks of adalimumab treatment (p=0.021), and its incensement was more apparent at week 24 (p=0.016). *P*-values are given in Table II.

Changes of MRI scores

The mean ± SD MRI scores of SIJs are shown in Table I. AS patients had a significant reduction in SPARCC MRI score of SIJs (p=0.001) after 12 weeks of adalimumab treatment, and at week 24, the mean value of MRI score of SIJs also dropped significantly as compared with baseline (p=0.000). *P*-values are given in Table II.

Associations between CDUS scores and clinical and MRI data

The CDUS scores of SIJs and peripheral enthesitis correlated positively with clinical assessments (including BASDAI, BASFI and CRP) in AS patients whether at baseline or at week 12 or at week 24 (all p<0.05). While the RI value of SIJs correlated negatively with BASDAI, BASFI, CRP and MRI score of SIJs at all visits (all p<0.05). The CDUS scores of SIJs also had a positive correlation with MRI score of SIJs during adalimumab treatment (all p<0.05). The r-value and corresponding p-value of Pearson's/Spearman's rank correlation coefficient are listed in Table IV.

Discussion

In this study, we monitored the effect of adalimumab on sacroiliitis and peripheral enthesitis in AS patients by colour Doppler ultrasonography, and compared the results of CDUS with clinical assessments and MRI data.

It has been demonstrated that signs of active sacroiliitis could be detected by the CDUS method. Arslan *et al*. reported that the RI values were significantly decreased in patients with active sacroiliitis compared with asymptomatic volunteers, and the RI values would increase after treatment (11). Unlü *et al*. also reported that a low RI value may indicate increased inflammation in AS patients (39). However, in that study, only 11 AS patients were investigated with 12 weeks of anti-TNF therapy and they only detected the arterial flow signs around SIJs. As the vascularity located in SIJs were complex, Zhu *et al*. reported that colour Doppler signal inside and around SIJs in active AS patients were both important in assessing the activity of disease (12). Thus, in our study, we recorded blood flow both inside and around SIJs and got similar results as the above mentioned studies. We found that the CDUS scores of SIJs decreased, while the corresponding RI values increased significantly after 12 weeks of treatment with adalimumab in AS patients, and this effect would maintain after 24 weeks of adalimumab therapy.

Few studies have dealt with the value of CDUS in diagnosing inflammatory sacroiliitis as compared with MRI. Klauser *et al*. reported that the contrast-enhanced CDUS with a sensitivity of 94% could be used to detect active sacroiliitis as compared with MRI (40). Research on comparing the results of

Table IV. Associations between CDUS scores and clinical and MRI data in AS patients during adalimumab treatment*.

	CDUS score of SIJs	RI value of SIJs	CDUS score of PE
Baseline			
BASDAI	0.236, 0.028	-0.315, 0.014	0.411, 0.025
BASFI	0.189, 0.016	-0.167, 0.033	0.335, 0.038
CRP (mg/l)	0.536, 0.012	-0.426, 0.024	0.328, 0.024
SIJs MRI score	0.246, 0.020	-0.342, 0.015	NA
Week 12			
BASDAI	0.107, 0.031	-0.277, 0.039	0.398, 0.024
BASFI	0.167, 0.038	-0.233, 0.042	0.416, 0.043
CRP (mg/l)	0.547, 0.024	-0.386, 0.037	0.469, 0.046
SIJs MRI score	0.014, 0.041	-0.011, 0.039	NA
Week 24			
BASDAI	0.078, 0.047	-0.101, 0.041	0.235, 0.039
BASFI	0.088, 0.046	-0.091, 0.048	0.139, 0.042
CRP (mg/l)	0.327, 0.038	-0.264, 0.036	0.367, 0.041
SIJs MRI score	0.022, 0.039	-0.021, 0.045	NA

*Values were: r-value, corresponding p-value of Pearson's or Spearman's rank correlation coefficient. CDUS: colour Doppler ultrasonography; AS: Ankylosing Spondylitis; SIJs: Sacroiliac Joints; RI: Resistive Index; PE: peripheral enthesitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; CRP: C-reactive protein; NA: not applicable.

CDUS with MRI during adalimumab treatment in AS patients has not been reported yet. In our study, we tried to analyse the correlationship between the CDUS and MRI data. We found that the CDUS scores of SIJs positively related while the RI value negatively related with the MRI scores of SIJs no matter at baseline or after 12 weeks or 24 weeks of adalimumab therapy in AS patients. We confirmed that CDUS was able to reveal the changes of active sacroiliitis and could be used in follow-up during adalimumab treatment in AS patients.

The frequency of peripheral enthesitis has been found to be within 25–58% in patients with AS (41), and the prevalence of it depends on the type of assessment (*i.e.* clinical, imaging or histological). Among imaging techniques, musculoskeletal US has an increasing and relevant role in the assessment of AS. US may even detect the enthesitis that are clinically asymptomatic (37). Spadaro *et al*. reported that the rate of peripheral enthesitis was as high as 44.4% in AS patients, as detected by Doppler US (42). In our study, 53.7% of the 410 entheses of AS patients examined with CDUS at baseline showed abnormalities. The rate of peripheral enthesitis seem to be higher in our study, it may due to the disease status was active in the studied subjects. Unlü *et al*. reported that 12 weeks of treatment with infliximab or etanercept (other types of TNF-α blocking agent) could reduce vascularisation in AS patients as seen by CDUS (39). According to our data, the CDUS scores of peripheral enthesitis also dropped significantly after 12 weeks of adalimumab treatment. Moreover, we showed that the effect of adalimumab in reducing peripheral enthesitis maintained after 24 weeks of treatment, and the CDUS scores of sacroiliitis and peripheral enthesitis in this study correlated well with clinical assessments such as BASDAI, BASFI, and CRP. Thus, CDUS can reflect the disease activity of AS patients, especially in detecting the response to adalimumab.

There were several limitations in this study. Firstly, the number of patients included into the research was relatively small. Adalimumab was quite expensive to Chinese patients, and most of patients could not afford long term usage. Larger study sample and longer follow-ups would be needed in future research. Secondly, we did not include healthy controls in this study. We focused on the effect of adalimumab to AS patients. The use of adalimumab in healthy subjects would be unethical. Thirdly, we did not record other clinical indexes which may also be valuable to AS (such as AS Disease Activity Score-CRP and erythrocyte sedimentation rate), nor did we record the symptom of peripheral arthritis at the visits either. Future studies which include more clinical indexes could be done to explore the efficacy of adalimumab to AS better.

In conclusion, we found that CDUS could be used to monitor the changes of sacroiliitis and peripheral enthesitis in AS patients under adalimumab treatment. Moreover, the results of CDUS correlated well with clinical indices and MRI data.

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