

# A quick decrease of bone marrow edema in sacroiliac joint could be served as a novel marker for dose tapering of etanercept in ankylosing spondylitis patients

Ruishan Yang, BS<sup>a,\*</sup>, Hongda Liu, MM<sup>b</sup>, Mengpo Fan, MD<sup>c</sup>

## Abstract

The purpose of this study was to investigate the correlation of bone marrow edema (BME) in sacroiliac joint (SIJ) with clinical characteristics and clinical response, and whether the quick decrease of BME could be served as a novel marker for dose tapering of etanercept in ankylosing spondylitis (AS) patients.

Ninety active AS patients underwent etanercept treatment for 6 months were enrolled consecutively and classified into standard dose group ( $n=37$ ) and dose tapering group ( $n=53$ ). BME in SIJ and clinical response were assessed by SPARCC criteria and ASAS 40 response criteria, respectively. "Quick decrease of BME in SIJ" was defined as the decrease of SPARCC score  $\geq 50\%$  from M0 to M1.

BME in SIJ was positively correlated with pain VAS score, BASDAI score, CRP, IL-1 $\beta$ , IL-17, and TNF- $\alpha$  levels. ASAS 40 response rate at M6 was lower in dose tapering group than standard dose group, while higher in patients with a quick decrease of BME in SIJ than other patients. Besides, the ASAS 40 response rate in dose tapering group was similar to standard dose group in patients with a quick decrease of BME in SIJ but was lower than standard dose group in patients without a quick decrease of BME in SIJ at M6.

A quick decrease of BME in SIJ predicts better treatment response to etanercept, and it might be served as a novel marker for dose tapering initiation of etanercept in AS patients.

**Abbreviations:** AEs = adverse effects, AS = ankylosing spondylitis, ASAS = Ankylosing Spondylitis International Society, ASAS = assessment in ankylosing spondylitis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BME = bone marrow edema, CRP = C-reactive protein, ELLSA = enzyme-linked immunosorbent assay, ESR = erythrocyte sedimentation rate, HLA = human leukocyte antigen, IL-1 $\beta$  = interleukin 1 $\beta$ , IL-17 = interleukin 17, IL-6 = interleukin 6, MRI = magnetic resonance imaging, NSAIDs = nonsteroidal anti-inflammatory drugs, PGA = patient global assessment, RA = rheumatoid arthritis, SIJ = sacroiliac joint, SPARCC = Spondyloarthritis Research Consortium of Canada, STIR = short inversion time inversion recovery, TNF = tumor necrosis factor, VAS = visual analogue scale.

**Keywords:** ankylosing spondylitis, bone marrow edema, dose tapering strategy, etanercept, sacroiliac joint

## 1. Introduction

Ankylosing spondylitis (AS) is a severe autoimmune disease characterized by sacroiliitis, enthesitis, and anterior uveitis, which brings in great pain and functional disability to patients.<sup>[1,2]</sup> AS affects 0.23% of Chinese and 0.9%–1.4% of

American adults, and there is still no curable treatment for AS until now.<sup>[1,3–5]</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for alleviating pain and stiffness in AS patients; however, up to 20% of AS patients reveal no response to NSAIDs, and continuous use of NSAIDs may cause unacceptable adverse effects (AEs).<sup>[6]</sup> Worse still, glucocorticoids and conventional disease-modifying antirheumatic drugs that are commonly used in other rheumatic disease are seldom applied in AS treatment owing to the lack of adequate response.<sup>[3,7]</sup> Therefore, it remains a huge challenge to AS treatment.

As a 75 kD tumor necrosis factor (TNF) receptor fusion protein is linked to the Fc portion of human immunoglobulin G (IgG) subclass 1 (TNFr:Fc), etanercept is effective in treating AS patients who are intolerant or have no response to NSAIDs through acting as a recombinant human tumor necrosis factor (TNF- $\alpha$ ) inhibitor.<sup>[4,8–10]</sup> In spite of the superior efficacy of etanercept compared to NSAIDs in AS treatment, the high cost and the increased risk of AEs such as tuberculosis and bacterial infections under a recommended regimen of 50 mg/week trouble a lot of AS patients. Recently, a number of studies report that the 25 mg/week dose of etanercept is also effective in maintaining remission for AS patients.<sup>[11–16]</sup> However, a considerable percentage of patients in these studies relapse when dose tapering to 25 mg/week.<sup>[17,18]</sup> which indicates that not all AS patients are

Editor: Angelo Valerio Marzano.

The authors have no funding and conflicts of interest to disclose.

<sup>a</sup> Department of CT/MRI, The Second People's Hospital of Liaocheng, Linqing, Shandong, <sup>b</sup> Foot and Ankle Surgery, The Second Hospital of Tangshan, Tangshan, Hebei, <sup>c</sup> Department of Orthopaedic Surgery, The Second People's Hospital of Liaocheng, Linqing, Shandong, China.

\* Correspondence: Ruishan Yang, Department of CT/MRI, The Second People's Hospital of Liaocheng, Linqing 252600, Shandong, China (e-mail: yyyanghua@126.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:11(e14620)

Received: 25 October 2018 / Received in final form: 28 January 2019 /

Accepted: 29 January 2019

<http://dx.doi.org/10.1097/MD.00000000000014620>

suitable for dose tapering strategy of etanercept treatment. Thus, it is essential to explore novel and convincing markers for dose tapering of etanercept in treating AS patients.

Bone marrow edema (BME) is defined as an area of altered signal on the magnetic resonance imaging (MRI) of the bone, with the capacity to assess the disease activity and inflammation level in joint diseases.<sup>[19,20]</sup> Notably, BME in sacroiliac joint (SIJ) is associated with histological inflammation, disease activity, and radiographic progression, and it could predict clinical response to TNF inhibitor therapy in patients with spondyloarthritis including AS.<sup>[20–24]</sup> Thus, we hypothesized that BME in SIJ might also be used as a new marker for dose tapering strategy of etanercept treatment in AS patients. Therefore, the purpose of this study was to investigate the correlation of BME in SIJ with clinical characteristics and clinical response, and most importantly, to explore whether its quick decrease could be served as a novel marker for dose tapering of etanercept in AS patients.

## 2. Materials and methods

### 2.1. Patients

Ninety patients with active AS who underwent TNF inhibitor (etanercept) treatment at The Second People's Hospital of Liaocheng between 2014/1/1 and 2016/12/31 were consecutively enrolled in this prospective cohort study. The inclusion criteria included: (1) Diagnosed as AS according to 2010 Ankylosing Spondylitis International Society (ASAS) criteria;<sup>[25]</sup> (2) At active disease condition defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score > 4.0; (3) Age above 18 years; (4) About to receive etanercept treatment; (5) Able to be followed up regularly. The exclusion criteria consisted of: (1) Patients with contraindications of etanercept (such as active tuberculosis, invasive fungal infections, bacterial, viral, and other infections due to opportunistic pathogens, lymphoma and other malignancies, and so on); (2) Received biologics treatment (including etanercept) within 3 months; (3) Received glucocorticoid treatment within 1 month; (4) History of SIJ or spine surgery; (5) Pregnant or lactating women.

### 2.2. Ethics

This study protocol was approved by the Ethics Committees of The Second People's Hospital of Liaocheng and performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consents before participating in the present study.

### 2.3. Baseline data collection and assessments

After patients signed the informed consents, baseline characteristics were collected including age, gender, and diseases duration; meanwhile, the levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also measured and recorded. In addition, the Patient Global Assessment (PGA) score, pain Visual Analogue Scale (VAS) score, BASDAI score, and Bath Ankylosing Spondylitis Functional Index (BASFI) score were used to evaluate the disease activity of patients.

### 2.4. Measurement of inflammatory cytokines

Blood samples were collected from all patients before initiating etanercept treatment and allowed to clot for 20 to 30 min at room temperature followed by centrifugation at 2500 rpm for 5 min to

separate serum. Then the levels of interleukin 1 $\beta$  (IL-1 $\beta$ ), interleukin 6 (IL-6), interleukin 17 (IL-17), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in serum were detected by enzyme-linked immunosorbent assay (ELISA) kit (Abcam, USA) following the manufacturer's protocol.

### 2.5. Treatment and groups

According to disease condition and personal willingness, 135 AS patients received etanercept treatment, and patients who lost follow-up ( $n=34$ ) or withdrew the study before completion of 6-month etanercept treatment ( $n=11$ ) were excluded from the final analysed population, while 4 patients who withdrew the study due to the lack of efficacy were included into the analysis; thus, total 90 patients were included into the final analysis in this present study. Among all the 90 AS patients, 37 cases sustainably received subcutaneous injection of etanercept 25 mg twice a week for 6 months, which were classified into standard dose group; while another 53 cases received subcutaneous injection of etanercept 25 mg twice a week for 1–3 months, and subsequently received subcutaneous injection of etanercept 25 mg once a week for the remaining duration until 6 months, which were classified into dose tapering group.

### 2.6. Evaluation of bone marrow edema (BME) in SIJ

MRI scan of SIJ was performed at baseline (M0), month 1 (M1), M3 and M6 using T2 weighted imaging and short inversion time inversion recovery (STIR) sequence, and the Spondyloarthritis Research Consortium of Canada (SPARCC) score was used to evaluate BME in SIJ, which was independently scored by two experienced experts who did not know the subjects' clinical characteristics. In brief, the SPARCC score of SIJ was assessed as follows:<sup>[26]</sup> There were 12 layers consecutively scanned in total, and 6 layers were chosen from 4th to 9th layers to be scored in 3 aspects: (1) Involved area: SIJ of every layer in both sides was divided into 4 quadrants including upper iliac, lower iliac, upper sacral, and lower sacral. 1 point would be added if the area with BME (high signal) and 0 points were added if not, and total points of 6 layers would be 48 points. (2) Edema intensity: Joints that included a lesion exhibiting intense signal were each given an additional score of 1 per layer, and the total points would be 12 in 6 layers. (3) Edema depth: 1 point would be added if the edema depth of lesion exceeded 1 cm in every layer, and the total points would be 12 points. Total SPARCC scoring of SIJ was obtained by summing the involved area scoring, edema intensity scoring, and edema depth scoring, which ranged from 0 to 72 points. "Quick decrease of BME in SIJ" was defined as the decrease of SPARCC score of SIJ from M0 to M1 no less than 50% in this study.

### 2.7. Evaluation of treatment response

The Assessment in Ankylosing Spondylitis (ASAS) 40 response criteria was used to evaluate the clinical response to etanercept at M1, M3, and M6, which included following 4 domains: (1) Patient's global VAS score of disease activity; (2) VAS score of total pain in the spine due to AS and pain in the spine at night due to AS; (3) BASFI score; (4) Mean VAS score of items 5 and 6 of the BASDAI about morning stiffness duration. And ASAS 40 was defined as at least 40% improvement and 20 units of absolute change in 3 of 4 domains, without any worsening in the remaining domain.<sup>[27]</sup>

**Table 1****Baseline characteristics of active AS patients.**

Items	Total active AS patients (N=90)	Dose tapering group (N=53)	Standard dose group (N=37)	P value
Age (years)	27.9±6.5	27.6±6.3	28.4±6.8	.556
Gender (male/female)	76/14	43/10	33/4	.299
Disease duration (years)	5.4±3.2	5.5±3.2	5.4±3.2	.917
PGA score	6.1±1.7	5.8±1.7	6.5±1.7	.080
Pain VAS score	6.3±1.5	6.2±1.6	6.3±1.5	.727
BASDAI score	6.1±1.2	6.1±1.2	6.2±1.2	.614
BASFI score	5.1±1.3	4.9±1.1	5.3±1.4	.103
CRP (mg/L)	24.0 (18.7–32.5)	23.2 (18.9–29.9)	26.3 (18.1–37.5)	.217
ESR (mm/h)	25.0 (21.2–32.5)	23.3 (19.5–30.9)	26.2 (21.1–35.6)	.084
IL-1β (pg/mL)	5.2 (4.4–6.4)	5.1 (4.1–6.2)	5.3 (4.6–7.1)	.248
IL-6 (pg/mL)	35.5 (27.0–50.2)	33.8 (28.2–50.1)	37.7 (26.8–53.8)	.951
IL-17 (pg/mL)	50.0 (29.7–70.3)	39.3 (28.9–65.9)	54.7 (35.0–72.4)	.179
TNF-α (pg/mL)	44.0 (36.8–56.2)	42.7 (37.0–51.8)	45.3 (36.6–59.6)	.547
BME in SIJ (n/%)	61 (67.8)	35 (66.0)	26 (70.3)	.672
SPARCC score of SIJ	10.3±8.3	9.7±8.1	11.1±8.6	.424

Data were presented as mean value±standard deviation, median (quartile 25th–75th), or count (%). Comparison was determined by t test, Wilcoxon rank sum test or Chi-square test. *P* value < .05 was considered significant. AS=ankylosing spondylitis, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BME=bone marrow edema, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, IL-1β=interleukin 1β, IL-17=interleukin 17, IL-6=interleukin 6, PGA=Patient Global Assessment, SIJ=sacroiliac joint, SPARCC=Spondyloarthritis Research Consortium of Canada, TNF-α=tumor necrosis factor-α, VAS=Visual Analogue Scale.

## 2.8. Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (IBM, USA) and GraphPad Prism 6.01 software (GraphPad Software Inc, USA). Data were presented as mean value±standard deviation, median (quartile 25th–75th), or count (%). For normally distributed data, comparison between two groups was determined by t test (such as age, disease duration, and PGA score); correspondingly, pre- and post-treatment comparisons were performed by paired t test (such as SPARCC score of SIJ in total active AS patients). For the continuous non-normal data, comparison between two groups was determined by Wilcoxon rank sum test (such as CRP, ESR, and IL-6 levels). As for categorical variable data, the difference between two groups was examined using Chi-square test (such as gender, percentage of patients with BME in SIJ, and percentage of patients with ASAS 40), and the comparison at paired time point was performed with the use of McNemar test (such as percentage of patients with BME in SIJ in total active AS patients). *P* < .05 was considered significant.

## 3. Results

### 3.1. Baseline characteristics

No difference of demographic or clinical characteristics was observed between dose tapering group and standard dose group as shown in Table 1. The mean values of age in dose tapering group and standard dose group were 27.6±6.3 years and 28.4±6.8 years, respectively (*P*=0.556). There were 43 males and 10 females in dose tapering group, and 33 males as well as 4 females in standard dose group (*P*=0.299). The mean BASDAI score (*P*=.614) and BASFI score (*P*=.103) were 6.1±1.2 and 4.9±1.1 in dose tapering group and were 6.2±1.2 and 5.3±1.4 in standard dose group, respectively. Meanwhile, median CRP (*P*=0.217) and ESR (*P*=.084) in dose tapering group were 23.2 (18.9–29.9) mg/L and 23.3 (19.5–30.9) mm/h and were 26.3 (18.1–37.5) mg/L as well as 26.2 (21.1–35.6) mm/h in standard dose group, respectively. Other detailed clinical characteristics were depicted in Table 1.

### 3.2. Correlation of BME in SIJ with clinical characteristics of active AS patients

BME in SIJ was positively correlated with pain VAS score (*P*=.007), BASDAI score (*P*=.010), CRP (*P*=.008), IL-1β (*P*=.013), IL-17 (*P*=.012), and TNF-α (*P*=.011) in AS patients (Table 2). However, no association of BME in SIJ with other demographic and clinical characteristics was observed (all *P* > .05).

### 3.3. SPARCC score and the percentage of patients with BME in SIJ after treatment

The SPARCC score of SIJ in total active AS patients was decreased at M1 (*P* < .001), M3 (*P* < .001), and M6 (*P* < .001) compared to that of M0 (Fig. 1A). While the SPARCC score of SIJ in dose tapering group was similar to that in standard dose group at each visit (all *P* > .05, Fig. 1B). Meanwhile, the percentage of patients with BME in SIJ in total active AS patients was reduced at M1 (*P* < .05), M3 (*P* < .001), and M6 (*P* < .001) compared to that at M0 as well (Fig. 1C). However, there was no difference of the percentage of patients with BME in SIJ between dose tapering group and standard dose group at each visit (all *P* > .05, Fig. 1D).

### 3.4. Percentage of patients achieving ASAS 40 response after treatment

The percentages of patients realizing ASAS 40 response in total active AS patients at M1, M3, and M6 were 32.2%, 57.8% and 63.3%, respectively (Fig. 2A). No difference was found regarding the percentage of patients with ASAS 40 between dose tapering group and standard dose group at M1 (*P* > .05) or M3 (*P* > .05), whereas the percentage of patients with ASAS 40 response in dose tapering group was decreased compared to that in the standard dose group at M6 (*P* < .05) (Fig. 2B).

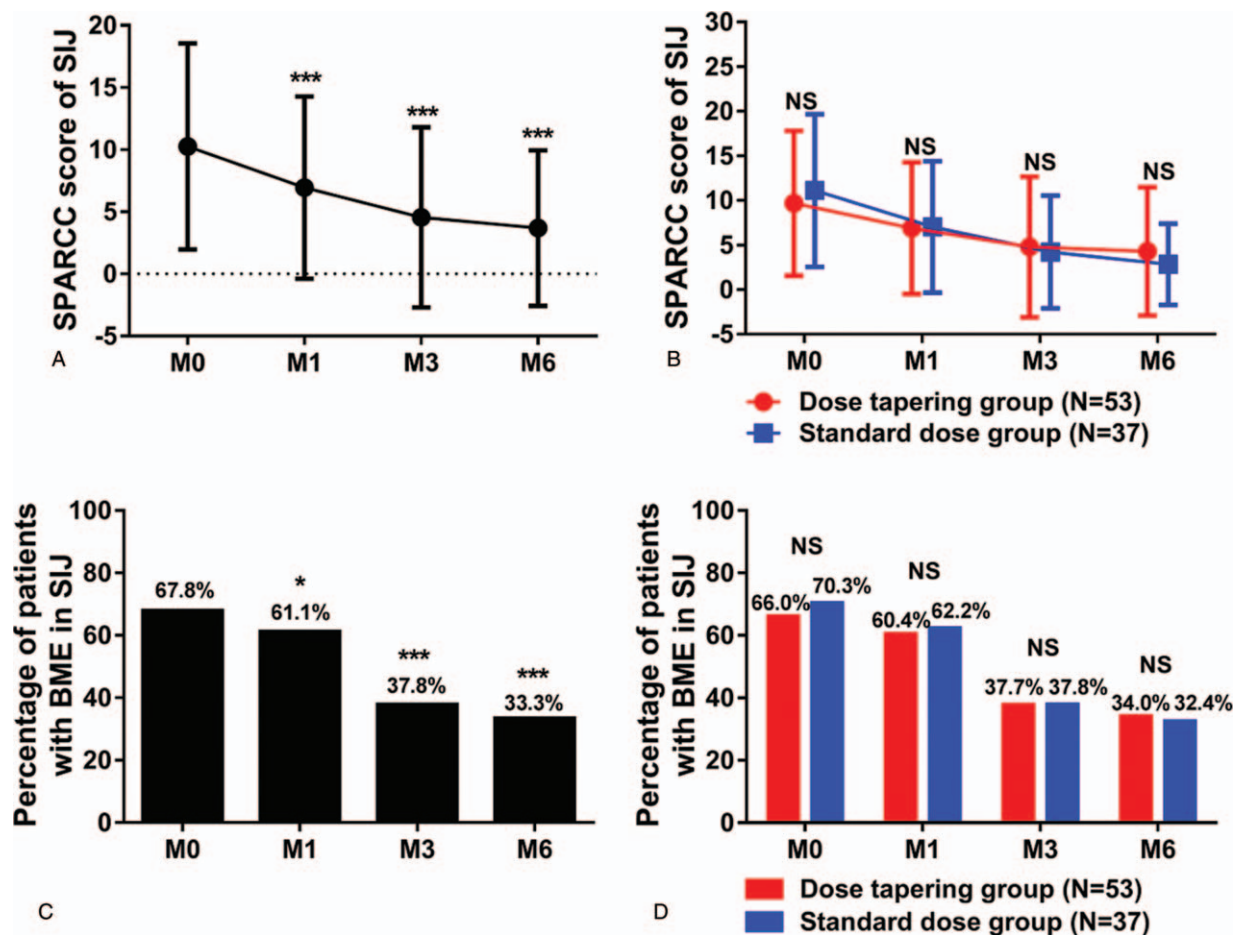
### 3.5. The correlation of BME and the quick decrease of BME in SIJ with ASAS 40 response

The ASAS 40 response rate was similar between patients with BME in SIJ and patients with non-BME in SIJ at M1 (*P* > .05),

**Table 2****Correlation of BME in SIJ with clinical characteristics of active AS patients.**

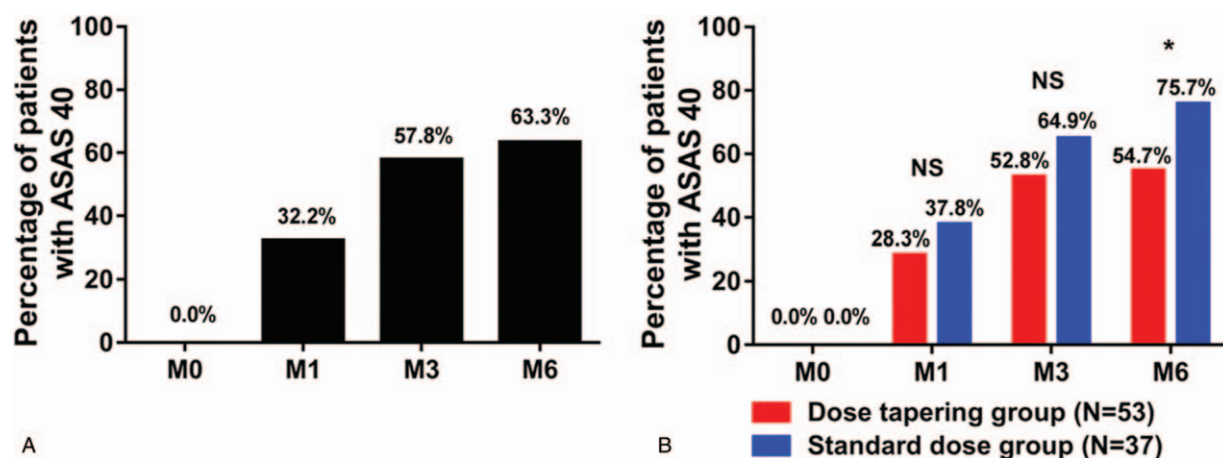
Items	BME in SIJ (N=61)	Non-BME in SIJ (N=29)	P value
Age (years)	27.1 ± 6.0	29.7 ± 7.3	.080
Gender (male/female)	52/9	24/5	.761
Disease duration (years)	5.2 ± 3.1	5.8 ± 3.4	.403
PGA score	6.3 ± 1.6	5.6 ± 1.7	.068
Pain VAS score	6.6 ± 1.4	5.6 ± 1.7	.007
BASDAI score	6.4 ± 1.2	5.7 ± 1.0	.010
BASFI score	5.3 ± 1.3	4.8 ± 1.2	.137
CRP (mg/L)	24.5 (20.5–34.1)	21.7 (15.8–28.7)	.008
ESR (mm/h)	26.2 (20.3–32.7)	23.3 (18.6–28.5)	.158
IL-1β (pg/mL)	5.4 (4.6–6.7)	4.7 (3.5–5.6)	.013
IL-6 (pg/mL)	38.8 (28.6–51.7)	32.6 (22.6–49.1)	.121
IL-17 (pg/mL)	52.2 (34.8–74.5)	36.4 (26.2–55.3)	.012
TNF-α (pg/mL)	47.2 (39.0–59.0)	39.0 (31.7–46.4)	.011

Data were presented as mean value ± standard deviation, median (quartile 25th–75th), or count. Comparison was determined by t test, Wilcoxon rank sum test or Chi-square test. *P* value < .05 was considered significant. AS = ankylosing spondylitis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BME = bone marrow edema, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IL-1β = interleukin 1β, IL-17 = interleukin 17, IL-6 = interleukin 6, PGA = Patient Global Assessment, SIJ = sacroiliac joint, TNF-α = tumor necrosis factor-α, VAS = Visual Analogue Scale.



**Figure 1.** Variations of SPARCC score and the percentage of patients with BME in SIJ after treatment. The SPARCC score in SIJ (A) and the percentage of patients with BME in SIJ (C) in total active AS patients were reduced at M1, M3, and M6 compared to M0, while no difference of SPARCC score (B) or percentage of patients with BME (D) in SIJ between dose tapering group and standard dose group at M0, M1, M3, or M6 was observed. Comparison of SPARCC score of SIJ at baseline (M0) and after treatment (M1, M3, and M6) was determined by pair t test; comparison of SPARCC score of SIJ between dose tapering group and standard dose group was determined by t test; comparison of percentage of patients with BMI in SIJ at baseline (M0) and after treatment (M1, M3, and M6) was determined by McNemar test, and comparison of percentage of patients with BMI in SIJ between dose tapering group and standard dose group was determined by Chi-square test. *P* < .05 was considered significant.





**Figure 2.** The percentage of patients with ASAS 40 after treatment. The percentage of patients with ASAS 40 was numerically increased in a time-dependent manner (A), which was relatively lower in dose tapering group compared to standard dose group at M6 (B). Comparison between two groups was evaluated by Chi-square test,  $P < .05$  was considered significant.

while it was increased in patients with BME in SIJ compared to that in patients with non-BME in SIJ at M3 ( $P < .05$ ) and M6 ( $P < .05$ ) (Fig. 3A). And patients with a quick decrease of BME in SIJ exhibited a similar ASAS 40 response rates at M1 ( $P > .05$ ) and M3 ( $P > .05$ ), but a higher ASAS 40 response at M6 ( $P < .05$ ) compared to that of other patients (Fig. 3B).

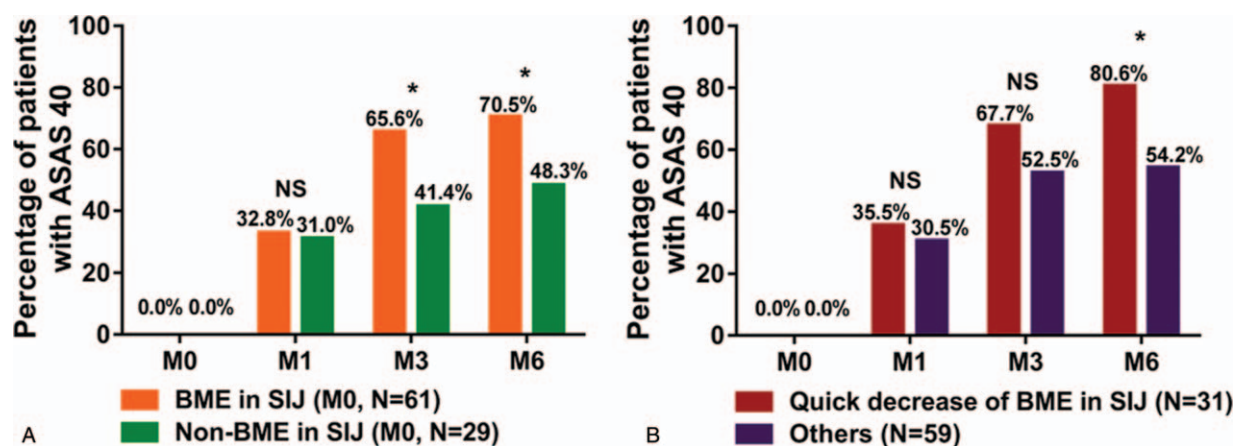
### 3.6. Comparison of ASAS 40 between dose tapering and standard dose treatments in subgroups

In patients with a quick decrease of BME in SIJ ( $N=31$ ), the ASAS 40 response rate in dose tapering group was similar compared to that in standard dose group at each visit (all  $P > .05$ , Fig. 4A). In patients without a quick decrease of BME in SIJ, the ASAS 40 response rate in dose tapering group was of no difference at M1 ( $P > .05$ ) or M3 ( $P > .05$ ), but reduced at M6 ( $P < .05$ ) compared to that in standard dose group (Fig. 4B).

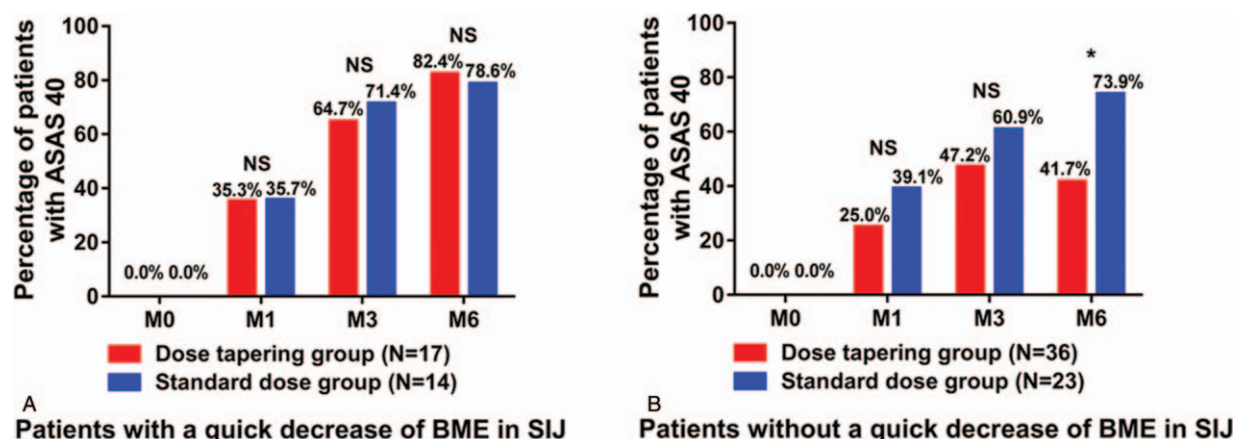
## 4. Discussion

In the current study, we discovered that in AS patients: (1) BME in SIJ was positively correlated with pain VAS score, BASDAI score, CRP, IL-1 $\beta$ , IL-17, and TNF- $\alpha$  levels. (2) BME in SIJ and disease activity were ameliorated post treatment, and the ASAS 40 response rate was lower in dose tapering group than in standard dose group at M6. (3) BME in SIJ and the quick decrease of BME in SIJ correlated with increased ASAS 40 response. (4) the quick decrease of BME in SIJ might be regarded as a marker for dose tapering of etanercept treatment.

BME commonly occurs in patients with joint inflammation such as rheumatoid arthritis (RA) patients and AS patients, which is observed to be associated with inflammation level, disease activity, joint damage, and bone erosion.<sup>[20,23,24]</sup> It is reported that RA patients with BME presented a higher ESR level compared to patients without BME.<sup>[19]</sup> Moreover, in patients with inflammatory back pain, the combination of positive human leukocyte antigen (HLA)-B27 with severe sacroiliitis (defined by



**Figure 3.** The correlation of the BME in SIJ or the quick decrease of BME in SIJ with the ASAS 40 response rate. The percentage of patients with ASAS 40 was larger in patients with BME in SIJ compared to patients with non-BME in SIJ at M3 and M6 (A). Meanwhile, the percentage of patients with ASAS 40 was increased at M6 in patients with a quick decrease of BME in SIJ compared to others (B). Comparison between two groups was assessed using Chi-square test,  $P < .05$  was considered significant.



**Figure 4.** Comparison of ASAS 40 response rate between subgroups after treatment. In patients with a quick decrease of BME in SIJ, no difference of the percentage of patients with ASAS 40 between dose tapering group and standard dose group was discovered at each visit (A), while in patients without a quick decrease of BME in SIJ, dose tapering group presented a lower percentage of patients with ASAS 40 compared to standard dose group at M6 (B). Comparison between two groups was determined by Chi-square test,  $P < .05$  was considered significant.

BME in SIJ) was a superb predictor for AS.<sup>[28]</sup> However, only a few studies exploring the correlation of BME in SIJ with inflammation level or disease activity in AS patients were conducted. In the current study, the BME in SIJ was positively associated with pain VAS score, BASDAI score, CRP, IL-1 $\beta$ , IL-17, and TNF- $\alpha$  levels. The possible explanation for our result may be that the edematous marrow is full of inflammatory infiltrates containing macrophages, memory T cells, B cells, plasma cells, and osteoclasts, which subsequently led to the rise of the inflammation level and disease activity of AS.<sup>[23]</sup> As a consequence, AS patients with BME in SIJ exhibited an elevated CRP, IL-1 $\beta$ , IL-17, and TNF- $\alpha$  levels, as well as higher VAS score and BASDAI score.

As one of the frequently used TNF- $\alpha$  inhibitors for AS patients, etanercept has been extensively investigated in its dosage adjustment strategy and corresponding efficacy.<sup>[29–32]</sup> Several studies suggest that tapering dose of etanercept is capable of keeping the remission after the standard treatment does in AS patients, but still a proportion of patients fail to maintain response to the tapering dose.<sup>[17,18]</sup> In the present study, the dose tapering group and the standard dose group were similar in decreasing the SPARCC score and the percentage of patients with BME in SIJ at each visit, whereas the percentage of patients achieving ASAS 40 response in dose tapering group was lower than that of standard dose group after 6-month etanercept treatment; these results might result from that (1) most diminishment of BME in SIJ occurred in the first 3-month while dose tapering of etanercept was moajoritly applied at or after 3 months; meanwhile, standard dose group illuminated a numerically higher SPARCC score than dose tapering group; thus, SPARCC score and the percentage of patients with BME in SIJ were of no difference between dose tapering group and the standard dose group after treatment. (2) As to ASAS 40 response, it was a comprehensive score assessing the absolute change of several indexes, and standard dose group disclosed numerically higher disease activity or functional score compared to dose tapering group, which increased the gap for deminishment; meanwhile, dose tapering presented with relatively lower efficacy than standard dose in a proportion of patients; thus, we found ASAS 40 response rate was reduced in dose tapering group than standard dose group.

The Berlin MRI spine score  $\geq 11$  (defined by BME grades) is discovered to be a predictor for BASDAI 50 response to TNF- $\alpha$  inhibitors in active AS patients, implying that BME might be applied for predicting clinical response to TNF- $\alpha$  inhibitors in AS patients.<sup>[22]</sup> As to the correlation of BME in SIJ with treatment response, only a study is reported, which discovers that sacroiliitis (defined by BME) on MRI is unable to predict clinical response to TNF- $\alpha$  inhibitor in AS patients, though the study assesses the efficacy of TNF- $\alpha$  inhibitor only for 14 weeks treatment.<sup>[33]</sup> In the present study, we found that patients with BME in SIJ assessed by SPARCC score presented with an elevated ASAS 40 response rate at M3 and M6 compared to that of patients with non-BME in SIJ. Furthermore, patients with a quick decrease of BME in SIJ also exhibited an increased ASAS 40 response rate at M6 compared with other patients. The possible explanation might be that BME in SIJ was positively associated with elevated level of inflammation; thus, patients with BME in SIJ were more likely to benefit from TNF- $\alpha$  inhibitors; as a result, those patients exhibited higher ASAS 40 response rate compared with patients with non-BME in SIJ.<sup>[19,20,23,24]</sup> As in patients with a quick decrease of BME in SIJ, the quick decrease of BME could be regarded as a superb clinical response of etanercept in AS patients. Therefore, patients with a quick decrease of BME were also displayed higher ASAS 40 response rate than other patients.

To further explore the potential of quick decrease of BME in SIJ as marker for dose tapering of etanercept in AS patients, we compared ASAS 40 response rate between dose tapering group and standard dose group in patients with or without a quick decrease of BME in SIJ, respectively. The results revealed that there was no difference of ASAS 40 response rate between dose tapering group and standard dose group in patients with a quick decrease of BME in SIJ, whereas in patients without a quick decrease of BME in SIJ, dose tapering group showed a lower ASAS 40 response rate at M6 compared to standard dose group. These indicated that a quick decrease of BME in SIJ might be served as a marker for dose tapering initiation of etanercept in AS patients. The possible reason might be that: As described above, patients with BME in SIJ showed increased pain VAS score, BASDAI score, CRP, IL-1 $\beta$ , IL-17, and TNF- $\alpha$  levels compared to patients without BME in SIJ; thus, the quick decrease of BME might indicate rapid decline of disease activity and inflammation

level, and most importantly, it reflected better response to treatment; thus, in this circumstance, AS patients were less affected by dose tapering of etanercept.

There were some limitations in this study. First, the study was single-centered, patients were mainly recruited from East China, which might cause selection bias. Second, clinical response of AS patients in the current study was only evaluated for six months; therefore, the long-term efficacy was not known. At last, the sample size in this study was relatively small, which might decrease statistical power.

In summary, a quick decrease of BME in SIJ predicts better treatment response to etanercept, and it might be served as a novel marker for dose tapering initiation of etanercept in AS patients.

## Author contributions

**Conceptualization:** Ruishan Yang.

**Data curation:** Hongda Liu.

**Formal analysis:** Ruishan Yang.

**Methodology:** Ruishan Yang.

**Resources:** Mengpo Fan.

**Software:** Hongda Liu.

**Supervision:** Mengpo Fan.

**Writing – original draft:** Ruishan Yang.

**Writing – review & editing:** Ruishan Yang.

Ruishan Yang orcid: 0000-0001-6920-9089.

## References

- [1] Mohammadi H, Hemmatzadeh M, Babaie F, et al. MicroRNA implications in the etiopathogenesis of ankylosing spondylitis. *J Cell Physiol* 2018;5564–73.
- [2] Rezaeiamesh A, Abdolmaleki M, Abdolmohammadi K, et al. Immune cells involved in the pathogenesis of ankylosing spondylitis. *Biomed Pharmacother* 2018;100:198–204.
- [3] Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. *N Engl J Med* 2016;374:2563–74.
- [4] Damjanov N, Shehhi WA, Huang F, et al. Assessment of clinical efficacy and safety in a randomized double-blind study of etanercept and sulfasalazine in patients with ankylosing spondylitis from Eastern/Central Europe, Latin America, and Asia. *Rheumatol Int* 2016;36:643–51.
- [5] Ho H-H, Chen J-Y. Ankylosing spondylitis: Chinese perspective, clinical phenotypes, and associated extra-articular systemic features. *Curr Rheumatol Rep* 2013;15:344.
- [6] Navarro-Sarabia F, Fernandez-Sueiro JL, Torre-Alonso JC, et al. High-dose etanercept in ankylosing spondylitis: results of a 12-week randomized, double blind, controlled multicentre study (LOADET study). *Rheumatology* 2011;50:1828–37.
- [7] Braun J, Sieper J. Ankylosing spondylitis. *Lancet* 2007;369:1379–90.
- [8] Lee JH, Youn JI, Kim TY, et al. A multicenter, randomized, open-label pilot trial assessing the efficacy and safety of etanercept 50mg twice weekly followed by etanercept 25mg twice weekly, the combination of etanercept 25mg twice weekly and acitretin, and acitretin alone in patients with moderate to severe psoriasis. *BMC Dermatol* 2016;16:11.
- [9] Ruwaard J, l'Ami MJ, Marsman AF, et al. Comparison of drug survival and clinical outcome in patients with ankylosing spondylitis treated with etanercept or adalimumab. *Scand J Rheumatol* 2018;47:122–6.
- [10] Braun J, McHugh N, Singh A, et al. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50mg once-weekly and 25mg twice-weekly. *Rheumatology* 2007;46:999–1004.
- [11] Park JW, Yoon YI, Chang SH, et al. THU0211 low dose etanercept treatment for maintenance of clinical remission in ankylosing spondylitis: retrospective cohort study. *Ann Rheum Dis* 2015;74(Suppl 2):272.
- [12] Navarro-Compan V, Moreira V, Ariza-Ariza R, et al. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. *Clinical Rheumatol* 2011;30:993–6.
- [13] Moghimi J, Sheikhvatan M, Semnani V. The use of low-dose etanercept as an alternative therapy for treatment of ankylosing spondylitis: a case series. *Rheumatol Int* 2012;32:2271–4.
- [14] Li J, Wang X, Han Z, et al. Dose reduction of recombinant human tumor necrosis factor inhibitors (etanercept) can be effective in ankylosing spondylitis patients with synovitis of the hip in a Chinese population. *Int J Immunopathol Pharmacol* 2016;29:510–5.
- [15] Lee SH, Lee YA, Hong SJ, et al. Etanercept 25 mg/week is effective enough to maintain remission for ankylosing spondylitis among Korean patients. *Clin Rheumatol* 2008;27:179–81.
- [16] Lee J, Noh J-W, Hwang JW, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. *Clin Rheumatol* 2010;29:1149–54.
- [17] Yates M, Hamilton LE, Elender F, et al. Is etanercept 25 mg once weekly as effective as 50 mg at maintaining response in patients with ankylosing spondylitis? a randomized control trial. *J Rheumatol* 2015;42:1177–85.
- [18] De Stefano R, Frati E, De Quattro D, et al. Low doses of etanercept can be effective to maintain remission in ankylosing spondylitis patients. *Clin Rheumatol* 2014;33:707–11.
- [19] Narváez JA, Narváez J, de Albert M, et al. Bone marrow edema in the cervical spine of symptomatic rheumatoid arthritis patients. *Semin Arthritis Rheum* 2009;38:281–8.
- [20] Manara M, Varenna M. A clinical overview of bone marrow edema. *Rheumatismo* 2014;66:184–96.
- [21] Bennett AN, Marzo-Ortega H, Rehman A, et al. The evidence for whole-spine MRI in the assessment of axial spondyloarthritis. *Rheumatology* 2010;49:426–32.
- [22] Rudwaleit M, Schwarzlose S, Hilgert ES, et al. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. *Ann Rheum Dis* 2007;67:1276–81.
- [23] Kwiatkowska B. Significance of bone marrow edema in pathogenesis of rheumatoid arthritis. *Pol J Radiol* 2013;78:57–63.
- [24] Schett G. Bone marrow edema. *Ann N Y Acad Sci* 2009;1154:35–40.
- [25] Rudwaleit M, van der Heijde D, Landewé R, et al. The development of assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777.
- [26] Qin J, Zhu J, Zhang Y, et al. DWI and SPARCC scoring assess curative effect of early ankylosing spondylitis. *Open Med* 2016;11:52–8.
- [27] van der Heijde D, Dougados M, Davis J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum* 2005;52:386–94.
- [28] Bennett AN, McGonagle D, O'Connor P, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008;58:3413–8.
- [29] Berthelot JM, Varin S, Cormier G, et al. 25 mg etanercept once weekly in rheumatoid arthritis and spondylarthropathy. *Joint, bone, spine: revue du rhumatisme* 2007;74:144–7.
- [30] Senabre-Gallego JM, Santos-Ramirez C, Santos-Soler G, et al. Long-term safety and efficacy of etanercept in the treatment of ankylosing spondylitis. *Patient Prefer Adherence* 2013;7:961–72.
- [31] Cantini F, Niccoli L, Cassara E, et al. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. *Biologics* 2013;7:1–6.
- [32] Borrás-Blasco J, Gracia-Perez A, Rosique-Robles JD, et al. Clinical and economic impact of the use of etanercept 25 mg once weekly in rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis patients. *Expert Opin Biol Ther* 2014;14:145–50.
- [33] Pedersen MB, Hamilton-Dutoit SJ, Bendix K, et al. DUSP22 and TP63 rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study. *Blood* 2017;130:554–7.