# Efficacy and safety of ultrasound-guided local injections of etanercept into entheses of ankylosing spondylitis patients with refractory Achilles enthesitis

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# Abstract Objective

Enthesitis is one of the most common and specific manifestations of ankylosing spondylitis (AS). However, the treatment of enthesitis is still a challenge for rheumatologist so far, especially to those AS patients with serious enthesitis. This study aimed to evaluate the efficacy and safety of ultrasound (US)-guided local injection of etanercept into entheses of AS patients with refractory Achilles enthesitis.

# Methods

Twelve AS patients with severe unilateral refractory Achilles enthesitis were enrolled. Among them, 5 patients received US-guided local injection of etanercept and the other 7 received betamethasone. BASDAI, BASFI, VAS of the affected heel, the percentage of ASAS20 responders, CRP, ESR and any adverse events were recorded at baseline, 2, 4, 8 and 12 weeks after the treatment. US was also used to evaluate the corresponding entheses at baseline and every follow-up visit.

# Results

The BASDAI, BASFI, VAS of the affected heel, CRP, ESR, the percentage of ASAS20 responders and the regional blood flow signals detected by colour Doppler were all improved in both the etanercept group and the betamethasone group, at each follow-up visit compared to the baseline data (p<0.05). There were no significant differences in the improvements of any of the above parameters between the two groups (p>0.05). In addition, there were no adverse events from the etanercept group, except for the mild acid bilges feeling during the injection procedure, while 1 patient from the betamethasone group developed mild local atrophoderma since the week 4 follow-up visit and the atrophoderma kept stable at the 2 subsequent visits.

# Conclusion

US-guided local injection of etanercept might be a highly effective, safe and well tolerated treatment for Achilles enthesitis in patients with AS.

Key words

ankylosing spondylitis, etanercept, Achilles enthesitis, ultrasound

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This work was partly supported by Science and Technology Project of Guangdong Province, China (no. 2009B080701034) and 5010 Clinical Research Projects of Sun Yat-Sen University, Guangzhou, China (no. 2007023).

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in revised form on March 8, 2011.

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Competing interests: none declared

#### Introduction

Enthesitis is inflammation of the entheses, the sites where tendons, ligaments or articular capsules insert into the bone. It is the primary feature of ankylosing spondylitis (AS) and usually involves the lower limb entheses such as the Achilles enthesis. Enthesitis always manifests as pain, protracted stiffness and soft tissue swelling (1). However, AS patients with enthesitis receiving traditional treatments including the application of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) could only obtain mild-to-moderate benefit in previous studies (2-4). Recently, tumour necrosis factor (TNF)- $\alpha$  inhibitors such as infliximab and etanercept, have been widely used to cure many rheumatic diseases including rheumatoid arthritis (RA) and AS. Although TNF- $\alpha$  inhibitors have revealed miraculous efficacy in decreasing the disease activity and increasing the physical function of AS patients, whether they could achieve complete remission of enthesitis was still controversial (5, 6). Moreover, the high costs and the underlying adverse effects, such as infection, administration reaction and increasing risk of malignancy, have also restricted their systemically widespread application in daily clinical work (7, 8).

Local therapy, such as local glucocorticoid injection into the inflammatory sites has been recommended for refractory enthesitis (9, 10) even though some physicians considered that local glucocorticoid injection might be harmful to the enthesis (11). Besides the local appilication of glucocorticoid, local injection of etanercept has recently been conducted by some researchers. For example, Cui et al. found that intra-articular injection of etanercept into the sacroiliac joint can improve the joint function and decrease the frequency of local enthesitis (12), and Bliddal et al. reported that intra-articular injection of etanercept with ultrasound (US) guidance in small-joint arthritis was safe and effective (13). These researches might shed some light on the local injection of etanercept to the management of severe enthesitis for AS patients. Never-

theless, to the best of our knowledge, since few reports have focused on local injection of etanercept and, so far, no research has been carried out on the direct injection of etanercept into the entheses, the efficacy and safety of local etanercept injection in the treatment of AS patients with refractory Achilles enthesitis deserve to be evaluated. Musculoskeletal US is a widely available, inexpensive technique and it can readily demonstrate superficial tissue inflammation (14). In addition, US might be superior to the magnetic resonance imaging in detecting early signs of enthesopathy (15). Furthermore, US was more sensitive and specific than laboratory or physical examination in the detection of enthesitis (16). Therefore, this study aimed to assess the efficacy and safety of US-guided local injection of etanercept into entheses in AS patients with refractory Achilles enthesitis using both clinical and US parameters.

#### Methods

## Patients

Twelve AS patients who met the 1984 modified New York criteria (17) and suffered from unilateral Achilles enthesitis were enrolled in this study. They all manifested with severe tenderness and swelling at the affected Achilles entheses with a score  $\geq 4$  on a visual analogue scale (VAS) in spite of continuously taking NSAIDs and sulfasalazine for at least 3 months, and all the corresponding entheses under evaluation were satisfied with the outcome measures in rheumatology clinical trials (OMERACT) preliminary definition of enthesopathy (18). In addition, patients who suffered from any other chronic diseases or acute infections during the 3 months before enrolment and patients with history of surgery or local injection of the the affected Achilles enthesis were excluded from this study. All participants had given their written informed consent in accordance with the Declaration of Helsinki before their enrolment.

#### Research protocol

In this 12-week study, patients were assigned to two groups according to their will and economic condition. For all12 patients, 5 received local injection of

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etanercept in the affected Achilles enthesis (etanercept group), and the other 7 patients received betamethasone (betamethasone group). The following clinical and disease activity parameters were evaluated at baseline, 2, 4, 8 and 12 weeks after treatment, respectively: VAS pain score of the affected heel, Bath AS disease activity index (BAS-DAI) (19), Bath AS functional index (BASFI) (20), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The percentages of the patients achieving an ASAS20 (21) response were calculated at each follow-up visits. US examinations, including B mode and colour Doppler were also carried out at baseline and every follow-up visit. Any adverse events were recorded during the whole study period. Besides the local injection, all patients continued their original treatment as usual during the research procedure.

# US evaluation

US evaluations were performed by a radiologist majored in musculoskeletal US. An  $\alpha$ -5 equipment (Aloka, Tokyo, Japan) with a 5-13 MHz probe was used. For each patient, Achilles entheses were examined bilaterally using the following procedure: first, the patient lay prone with the feet hanging over the edge of the examination table at 90° flexion. Then, gel was applied to the skin to provide an acoustic interface. Consequently, US was initially performed in B mode to detect morphologic abnormalities, and subsequently with colour Doppler mode to detect the vascularisation. The processing settings were held constant during the examination, and the temperature of the room was kept stable at 20°C. Each examination took about 10 minutes.

In B mode assessment, the following parameters were recorded during the examination procedure: retrocalcaneal bursitis, bony erosion, enthesophyte and the thickness of the entheses. Of the above parameters, retrocalcaneal bursitis, bony erosion and enthesophyte were defined according to Balint's suggestion (16): retrocalcaneal bursitis was defined as a well circumscribed, localised anechoic or hypoechoic area at the site of retrocalcaneal bursa and which was compressible by the transducer; bony erosion was defined as a cortical breakage with a step down contour defect; enthesophyte was a step up bony prominence at the end of the normal bone contour. The enthesis thickness was measured at the point of maximal thickness proximal to the bony insertion.

For colour Doppler, the settings used were pulse repetition frequency of 0.5– 1.0 kHz and dynamic range 50–55 dB, and low wall filter. The regional blood flow was visualised at a gain level without background noise. The vascularisations of the Achilles enthesis were detected and semi-quantitatively graded according to Kiris's protocol (22) which is shown in Table I.

## US-guided local injection

After US examination, US-guided local injection was performed by the same radiologist and an experienced rheumatologist. Firstly, patients were assigned to keep the same posture till the end. If the patient was from the etanercept group, 12.5 mg etanercept (CPGJ, Shanghai, China) was diluted by 1 ml sterile water, or 1 ml compound betamethasone (Merck, Whitehouse Station, USA) injection which contained 5mg betamethasone dipropionate and 2 mg betamethasone phosphate would be used for local injection. Then the skin was sterilised with iodophors and covered with a sterile paper sheet with a hole revealing only the Achilles enthesis. The US probe was held on the dorsal side of the Achilles entheses parallel with the fibres. Then, a local anesthesia of the skin and subcutaneous tissue by 2% lidocaine with a 25gauge needle was given and soon afterwords the needle was directly inserted into the related Achilles enthesis. After confirmation of the right position of the needle by injecting trace of 2% lidocaine, etanercept or betamethasone was slowly injected into the enthesis (Fig. 1). After treatment, the corresponding ankle was constrained from any movement for at least 1 hour. Then the Achilles tendon and entheseal integrity was confirmed by US re-evaluation and the patients were required to avoid any heavy loads on the related ankle as well as vigorous activity for a week.

#### Statistics

Differences of demographic features and basic clinical characteristics of patients between groups were tested by two-sided Fisher's exact test or Student's independent *t*-test. Differences of variables, including BASDAI, BASFI, VAS of the affected heel, ESR and CRP between groups and among different time points were compared using ANOVA with repeated measures (RMANOVA). Semi-quantitative grade of flow signal was compared through Kruskal-Wallis test. *P*-values less than 0.05 were considered statistically significant.

### Results

Demographic and clinical information For all the 12 patients enrolled in this study, 5 were assigned to the etanercept group and the other 7 to the betamethasone group. All 5 patients from the etanercept group were male and their mean age, disease duration and positive rate of HLA-B27 were 30.8±8.1 years, 8.8±7.2 years and 100.0%, respectively. While in the betamethasone group, 6 patients were male and 1 was female, mean age, disease duration and positive rate of HLA-B27 were 23.1±5.5 years, 6.1±5.7 years and 85.7%, respectively. The baseline disease activity para-

Table I. The semi-quantitative grade of vascularisation in the Achilles enthesis.

Grade	Description
1	No flow signal
2	Presence of separate dot signals or short linear signals
3	Presence of clearly discernible vascularity with either many small vessels or several long vessels with or without visible branching though involving less than half of the entheses
4	Severe flow signal refers to the presence of vessels involving more than half of the enthe- ses



**Fig. 1.** The procedure of ultrasound-guided injection into the Achilles enthesis. Longitudinal extended field of view sonographic images of the hindfoot demonstrated the process of local injection. A, C, AE, RB N denoted the Achilles tendons, calcaneus, Achilles enthesis, retrocalcaneal bursa and needle, respectively. (A) The Achilles tendons before injection. (B) A needle (arrow) was inserting into the Achilles enthesis, appearing as a hyperechoic punctiform reflector. Trace lidocaine was injected into the enthesis to confirm the position of the needle. (C) Under real-time monitoring, etanercept or betamethasone was locally injected into the enthesis. (D) The needle has been removed after the injection.

meters including BASDAI, BASFI, VAS of the affected heel, ESR and CRP are shown in Table II. There were no significant differences in gender constitute, age, disease duration, the positive rate of HLA-B27 and all the disease activity parameters mentioned above between the two groups (p>0.05).

## Clinical assessment

Both the patients from the etanercept and betamethasone group obtained dramatic improvement after local injection treatment (Table II). RMANOVA exhibited that in both groups the BASDAI, BASFI, VAS of the affected heel, ESR and CRP at week 2, 4, 8 and 12 followup visits improved with significant differences compared with their baseline data (p<0.05). It was noteworthy that all the parameters between the two groups were not significantly different (p>0.05), which implied that clinical efficacy between these two reagents was similar. In addition, the achievements of ASAS20 response at any follow-up visits were comparative between the two groups (Fig. 2, p>0.05).

#### US evaluation

Although most of the patients obtained clinical improvement, the morphological change detected by B mode US was not as obvious as the clinical disease activity parameters. There were no changes either for the bony erosion or enthesophyte in both groups. The thickness of the related Achilles entheses was slightly decreased after treatment but not significantly from baseline. Similarly, the number of retrocalcaneal bursitis of each group were decreased, but no difference was observed between groups or visits (Table III).

As to colour Doppler examination, vascularisation was detected in all patients at baseline, and the blood flow signals of most of the patients were classified as grade 3 or grade 4 regardless of which group they were from. In both groups, vascularisation gradually decreased after treatment, and most of the patients were classified as grade 1 or grade 2 at week 4, 8 and 12 follow-up visits (Table IV, Fig. 3). The blood flow signals of each group were both greatly improved at each follow-up visit after the local injection compared with baseline (p < 0.05), and the improvement was not significantly different between the etanercept and betamethasone groups (p > 0.05).

## Adverse effects

During the process of US-guided local injection, most of the patients from the two groups experienced mild acid bilges feeling when the solution was slowly injected into the Achilles enthe-

Table II. Clinical parameters at baseline and each follow-up visit of US-guided injection of etanercept or betamethasone in AS patients.

Parameters	Etanercept group (n=5)					Betamethasone group (n=7)				
	Baseline	Week 2	Week 4	Week 8	Week 12	Baseline	Week 2	Week 4	Week 8	Week 12
BASDAI*	$5.2 \pm 2.9$	$2.6 \pm 1.4$	2.1 ± 1.5	2.3 ± 1.8	$2.7 \pm 2.3$	5.2 ± 3.5	$2.1 \pm 1.4$	2.6 ± 1.8	$2.5 \pm 1.4$	2.8 ± 1.4
BASFI*	$4.1 \pm 3.6$	$2.3 \pm 1.7$	$1.8 \pm 1.7$	$1.8 \pm 1.5$	$2.6 \pm 1.9$	$4.4 \pm 3.4$	$1.7 \pm 1.7$	$2.0 \pm 2.4$	$2.7 \pm 2.2$	$2.9 \pm 2.7$
VAS*	$5.0 \pm 1.3$	$0.7 \pm 0.9$	$0.7 \pm 0.9$	$1.0 \pm 1.1$	$1.3 \pm 1.0$	$5.3 \pm 0.7$	$0.8 \pm 1.0$	$0.5 \pm 0.6$	1.1 ± 1.1	$1.5 \pm 0.8$
CRP (mg/L)*	$52.4 \pm 50.0$	$18.8 \pm 17.6$	$33.9 \pm 39.1$	$27.5 \pm 32.3$	$22.3 \pm 21.3$	$51.6 \pm 47.1$	$23.3 \pm 26.2$	$21.0\pm20.0$	$19.3 \pm 20.1$	$18.9 \pm 18.0$
ESR (mm/h)*	$48.6 \pm 22.3$	$21.6 \pm 15.2$	$19.8\pm22.0$	$18.4 \pm 19.8$	$15.6 \pm 15.0$	$47.1 \pm 21.7$	$20.7 \pm 14.6$	$16.4 \pm 10.9$	$15.4 \pm 12.6$	$14.3 \pm 10.1$

US: Ultrasound; BASDAI: Bath ankylosing spondylitis disease activity; BASFI: Bath ankylosing spondylitis functional index; VAS: Pain levels on a visual analogue scale; CRP: C-reactive protein; ESR: Erythrocyte sedimentation.

\*p<0.05 when compared between each follow-up visit and baseline, and p>0.05 when compared between the two groups.

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Parameters		Betamethasone group (n=7)								
	Baseline	Week 2	Week 4	Week 8	Week 12	Baseline	Week 2	Week 4	Week 8	Week 12
Thickness(mm)*	9.7±2.6	8.1±2.5	8.1±2.6	8.1±2.5	8.1±2.5	7.6±3.1	6.3±2.4	6.2±2.1	6.2±1.9	6.2±1.9
Bursitis(n)*	4	3	3	3	3	7	4	3	3	3
Bony erosion(n)*	1	1	1	1	1	4	4	4	4	4
Enthesophyte(n)*	1	1	1	1	1	1	1	1	1	1

Table III. US parameters at baseline and each follow-up visit of US-guided injection of etanercept or betamethasone in AS patients.

\*p>0.05 when compared between each follow-up visit and baseline, and p>0.05 when compared between the two groups.



Fig. 2. The percentages of patients achieving an ASAS20. p<0.05 when compared between each follow-up visit and baseline, and p>0.05 when compared between the two groups.

sis, but the discomfort soon eased up after the procedure. No acute Achilles tendons rupture was observed during the treatment process or by the US reevaluation 1 hour after the injection. During the 4 follow-up visits, one patient who received local injection of betamethasone developed mild local atrophoderma at the point of entry (Fig. 4) since Week 4 follow-up visit and the atrophoderma kept stable at the subsequent 2 visits, but he responded very well to this therapy and had no other noticeable adverse event. No other adverse events were seen in the remaining 11 patients, including the late-onset

Achilles tendons rupture, allergic reaction, related skin reaction and signs of local infection at the heel or their surroundings found by clinical and US examinations.

### Discussion

TNF- $\alpha$  contributes to the pathogenesis of AS through various mechanisms, so blocking TNF- $\alpha$  might theoretically decrease inflammation activity of AS patients. Practically, the widespread use of TNF- $\alpha$  inhibitor in recent years has greatly improved the clinical symptoms and signs, preserved functional status, and ameliorated quality of life of AS

patients, especially for those AS patients with a high level of disease activity in an early stage of AS (1). However, the effect of systemic administration of TNF- $\alpha$  inhibitor on enthesitis is still uncertain (6), and from our clinical experience, some AS patients with refractory Achilles enthesitis might obtain limited improvement of their local entheseal symptoms and signs even after they had received long-course systemic administration of TNF-a inhibitor. Furthermore, a series of serious adverse events were successively reported since more and more patients began to receive subcutaneous or intravenous administration of TNF- $\alpha$  inhibitors in recent years. On the other hand, the high costs also excluded many patients from receiving TNF- $\alpha$  inhibitor therapy (7, 8). On the contrary, local injection of TNF-a inhibitor in inflammatory enthesis might achieve a higher drug concentration in the enthesis, making it possibly more likely to achieve a complete remission of enthesitis, and more likelihood of functioning at a relatively low dose of TNF- $\alpha$  inhibitor when compared with systemic administration. As a result, local injection of TNF- $\alpha$  inhibitor might decrease not only the potential high risk of many severe adverse reactions, but also the patients' heavy burden on the economy. Thus, local etanercept injection might be a promising technique in

Table IV. The blood flow grade in Achilles enthesis at baseline and at each follow-up visit detected by colour Doppler.

Grade		(n=5)*		Betamethasone group (n=7)*						
	Baseline	Week 2	Week 4	Week 8	Week 12	Baseline	Week 2	Week 4	Week 8	Week 12
Grade 1 (n)	0	0	1	2	1	0	2	4	3	2
Grade 2 (n)	0	2	3	2	2	2	4	3	3	4
Grade 3 (n)	2	3	1	1	2	3	1	0	1	2
Grade 4 (n)	3	0	0	0	0	2	0	0	0	0

p < 0.05 when compared between each follow-up visit and baseline, and p > 0.05 when compared between the two groups.



**Fig. 3.** Blood flow signal changes in an Achilles enthesis of an ankylosing spondylitis patient who received etanercept local injection. The semi-quantitatively flow signal was grade 4, 3, 2, 2 and 2 at baseline (**A**), week 2 (**B**), week 4 (**C**), week 8 (**D**) and week 12 (**E**) follow-up visit, respectively.



(E)

the treatment of AS patients with refractory Achilles enthesitis, therefore the efficacy and safety of local etanercept injection deserve to be evaluated. Achilles enthesis has always been considered by some physicians as an out-of-bounds area for local injection because of its anatomical and histologi-

cal specificity. Tendon rupture might be the most serious adverse effect that could occur during the entheseal local injection process or after the treatment. Since Achilles entheses are very important for the motion of the ankles and the feet, once the Achilles tendon ruptures or breaks because of the puncture, there will be serious consequences on the movement of the ankles and feet. However, the highly specialised anatomy of Achilles enthesis not only places high potential risk for local injection, but might also provide some protection mechanisms for the operation. For instance, retrocalcaneal bursa which lies between the Achilles tendon and the posterior surface of the calcaneus might be enlarged during the process of local injection and plays the role of pressure dissipation (23). Kachlik et al. (24) reported that the volume of retrocalcaneal bursa was about 1~1.5 ml because it was completely covered by a soft synovial membrane and thus it could be extended under pressure. In addition, Kager's fat pad might minimise pressure changes in the retrocalcaneal bursa (25). Therefore, the safety of local injection in the Achilles entheses is still controversial. Nonetheless, strictly choosing the indications and taking great care during the operation process might also be very important to reduce potential adverse effects. On the other hand, repeated puncture over a short time may increase the risk of tendon rupture or break, so accuracy of puncture might be the key issue to reduce potential adverse effects related to local injection. In addition, US provides realtime imaging, making it a good tool for guiding minimally invasive procedures such as local injections, needle biopsies and aspiration. Thus, in this study, US was chosen to guide the injection so as to increase the accuracy of the puncture and to ensure that the injection was made exactly in the target position, concluding that guidance may help increase the efficacy and safety of local injection in Achilles enthesis.

Experiences in local administration of etanercept are still very limited so far, but based on the powerful anti-inflammatory effects of etanercept in treating AS patients and the importance of US guidance in helping increase the efficacy and safety of local injection, USguided local injections of etanercept were performed in unilateral Achilles entheses of 5 AS patients who suffered from refractory Achilles enthesitis. On the other hand, betamethasone is another powerful anti-inflammatory drug and is widely used in local injection to cure arthritis, tenosynovitis, scapulohumeral periarthritis and so on, so another group used betamethasone in US-guided local injection in unilateral Achilles entheses of 7 AS patients with refractory Achilles enthesitis was set as a control. As a result, the 12 AS patients obtained not only a clinical improvement, but also a decrease in the blood flow signal from both etanercept and betamethasone local injection, and efficacy from a single treatment could last as long as 12 weeks. Similar to our study, Fredberg et al. (26) gave peritendinous injections of adalimumab to 10 patients with symptomatic unilateral tendinopathy, and the treatment showed a significant effect on pain sensation at rest in chronic Achilles tendinopathy and a tendency to reduce the blood flow in the tendon over 12 weeks. In addition, Schatteman et al. (27) reported that 3 AS patients with relapsing arthritis of the knee obtained a clear improvement in clinical, biological variables as well as the MRI findings from intraarticular injections of infliximab, and the effects lasted as long as 3 months or even longer, so they considered that intraarticular injection of infliximab was effective and safe for refractory monoarthritis in AS patients. The preliminary results from our present research also implied that both etanercept and betamethasone local injections in the Achilles entheses might be effective for AS patients with refractory Achilles enthesitis.

As to side-effects, the potential adverse effects that have been reported for local injection of etanercept were local hypersensitivity reaction and infection (28, 29). But in this present study, no serious adverse effects including Achilles tendons rupture or break, allergic reaction and local infection were found during the injection procedure and the 12-week follow-up for all 5 patients. The only adverse effect found in the etanercept group was the mild acid bilge feeling during the injection procedure. While in the betamethasone group, besides the mild acid bilge feeling experienced by most of the patients during the injection procedure, 1 patient developed mild local atrophoderma at the point of entry after the treatment. The atrophoderma of local skin and subcutaneous tissue might be caused by betamethasone, especially the betamethasone dipropionate that leaked into the subcutaneous tissue because the entheses was dense and the tough connective tissue had poor ductility, leading to a decrease in the soft tissue fibrous matrix (28). Our preliminary study implied that local injection of etanercept might be safer than the application of betamethasone. Furthermore, research on animal models suggested that intratendinous corticosteroid adversely affects the biomechanical properties of tendons and corticosteroids could inhibit the formation of adhesions, granulation, and connective tissue, leading to tendon mass reduction and biomechanical integrity decrease (30). Therefore, local administration of etanercept in enthesis might be safer than the administration of betamethasone.

In conclusion, this study observed the efficacy and safety of US-guided local injections of etanercept into the entheses of AS patients with refractory Achilles enthesitis, and the results implied that US-guided local injection of etanercept might be a novel, promising, well-tolerated, highly effective and safe treatment for Achilles enthesitis in patients with AS. It may help to reduce the potential high risk in adverse effects and the heavy economic burden of systemic administration of TNF- $\alpha$  inhibitors. However, there were some potential limits of this study. For example, the small number of patients enrolled and the potential influence of patients' basic treatment on the results was not fully taken into account. Moreover, the follow-up period was not long enough to observe how long the effect would last, so further study should be carried out to clarify the exact significance of US-guided local injection of etanercept in the treatment of AS patients with Achilles enthesitis.

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