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ORIGINAL ARTICLE

Clinical and MRI response to dose reduction of an etanercept-biosimilar for hip arthritis in patients with ankylosing spondylitis: an observational, retrospective cohort study

Zhi-Xiang Huang[1] · Wei-Ming Deng[1] · Xin Guo[1] · Zheng-Ping Huang[1] · Yu-Kai Huang[1] · Chu-Lan Lin[2] · Tian-Wang Li[1]

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Abstract

Objectives Hip arthritis plays a critical role in the prognosis of ankylosing spondylitis (AS). Dose reduction of tumor necrosis factor inhibitors preserves general improvement of AS, so this study attempted to examine the equivalence between Yisaipu® tapering and conventional therapy for hip arthritis in AS patients, using clinical parameters and magnetic resonance image (MRI).

Methods AS patients received this etanercept-biosimilar injections (50 mg/week) in the first 12 weeks. Participants in the tapering group were treated with this reagent 50 mg every other week from week 13 to week 24, while the control group kept undergoing full-dose therapy. Clinical and laboratory parameters were assessed at baseline, week 12 and week 24. MRI examination of hip was performed at baseline and week 24.

Results One hundred and thirty-six patients were enrolled, and 80 of them were in the tapering group. Linear mixed model revealed that main effects of tapering group with control group as reference in disease activity parameters were insignificant ($p > 0.05$). Main effects of baseline with week 24 as reference were significant ($p < 0.05$), but main effects of week 12 with week 24 as reference were not ($p > 0.05$). Prevalence of acute inflammatory change in MRI significantly decreased in the tapering group (76.88% vs 20.00%, $p < 0.05$) and control group (76.79% vs 19.64%, $p < 0.05$). Influence of both treatments on acute inflammatory change was equivalent ($p > 0.05$).

Conclusion Efficacy of Yisaipu® tapering treatment is comparable to the full-dose therapy for hip arthritis in AS patients. Both treatments maintain remission of hip arthritis after patients achieved low disease activity.

Keywords Ankylosing spondylitis · Dose reduction · Etanercept-biosimilar · Hip · MRI

Introduction

Hip arthritis is a common disorder affecting approximately 10 to 50% of patients with ankylosing spondylitis (AS), due to the different definition of diagnosis in studies [1, 2]. Histological feature of hip arthritis in AS is synovitis, which shares pathological similarities with rheumatoid arthritis. Progressive synovitis induces bone erosion, joint space narrowing, and ankylosis of hip [3]. Therefore, hip arthritis can result in functional impairment and disability, which leads to hip replacement up to nearly 8% of AS cases with hip involvement [4].

Tumor necrosis factor inhibitors (TNFi) have revolutionized the management for AS [5]. These reagents relieve pain, improve physical function of hip, and decrease demand for joint replacement [1, 6]. Yet, conventional TNFi therapy in long-term contributes to heavy economic burden and increasing risk of adverse effect; hence, dose reduction is necessary for majority of patients [7]. Recent evidence suggests that etanercept tapering may preserve low disease activity or remission of hip arthritis in AS patients. Furthermore, its efficacy is comparable to full-dose of etanercept subcutaneous injection [8, 9]. Although these findings shed light on TNFi dose reduction in the treatment of hip arthritis, hip-related clinical parameter was rarely used in previous studies. In addition, no study monitors change of hip using magnetic resonance image (MRI), despite of its high sensitivity in detecting acute inflammatory lesion.

✉ Tian-Wang Li
litian-wang@163.com

[1] Department of Rheumatology and Immunology, Guangdong Second Provincial General Hospital, No. 466 Xingangzhong Road, Guangzhou 510317, China

[2] Department of Medical Imaging, Guangdong Second Provincial General Hospital, Guangzhou, China

Yisaipu® is a recombinant human soluble tumor necrosis factor receptor II: IgG Fc fusion protein, which has been regarded as an etanercept-biosimilar. This reagent is one of the most widely used TNFi in China [10]. Therefore, this study sought to examine the equivalence of clinical efficacy, and MRI features changes between this etanercept-biosimilar tapering and conventional therapy for hip arthritis in AS patients, after they achieved low disease activity or remission.

Methods

Study design and participants

This was a monocentric, observational, and retrospective cohort study. Medical records of 136 AS patients who met the 1984 modified New York criteria [11] and undertook Yisaipu® treatment between March 2013 and November 2018 were retrospectively reviewed. All patients received non-steroidal anti-inflammatory drug therapy for at least 3 months. However, they still had high or very high disease activity, according to AS disease activity score with C-reactive protein (ASDAS-CRP) [12]. The demographic and clinical data were collected before therapy, including gender, age, disease duration of AS, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ASDAS-CRP, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [13], Bath Ankylosing Spondylitis Functional Index (BASFI) [14], visual analogue scale (VAS) of bilateral hip pain levels [15], and Harris hip score (HHS) [16]. Positive rates of hip pain, peripheral joints involvement, uveitis, inflammatory bowel disease, psoriasis, enthesitis, dactylitis, human leukocyte antigen-B27, family history of AS, and the Patrick's test were recorded as well.

Before starting TNFi, all participants had undergone examinations for searching laboratory markers of tuberculosis, hepatitis B virus, hepatitis C virus, syphilis, and human immunodeficiency virus, in order to rule out any latent infection. Patients with malignancy, a recent history of malignant condition, or acute infection (< 1 month) were excluded. Pregnancy, breast feeding, a leukocyte count $< 3.5 \times 10^9$/L, and aspartate or alanine transaminase levels ≥ twofold the upper limit of normal range at baseline were also criteria for exclusion. We excluded patients who had undergone hip replacement surgery as well.

The starting dose of this etanercept-biosimilar was 50 mg/week from the baseline to week 12. If the patients had inactive or low disease activity in week 12 (ASDAS-CRP < 2.1), whether they undertook dose reduction or full-dose etanercept-biosimilar therapy were determined by the discussion between patients and physicians [17]. Eighty AS patients chose dose reduction (tapering group), and they received this etanercept-biosimilar 50-mg subcutaneous injections every other week from the week 13 to week 24. The other 56 patients maintained conventional dose of this etanercept-biosimilar treatment until week 24 (control group). Celecoxib at a dose of 200 mg twice per day was added to all patients during 24 weeks as background therapy. Adherence to celecoxib was measured using a 24-week medication possession ratio (MPR), which was calculated as (total prescription days / (last prescription date − the first prescription date)). Data was collected from prescription records in the pharmacy of our hospital. A MPR of ≥ 0.8 was accepted as good compliance [18].

Protocol approval

This study was approved by the ethics committee of Guangdong second provincial general hospital (2015-KLYY-0015). Written informed consents in accordance with the declaration of Helsinki were given by participants.

Clinical assessments

Serum CRP and ESR were measured at baseline, week 12 and week 24. ASDAS-CRP, BASDAI, BASFI, VAS of bilateral hip pain levels, and HHS were also recorded by an experienced rheumatologist at the same time.

Conventional radiography

Anteroposterior X-ray examinations for pelvic were performed at baseline and week 24. Each hip was scored using two different methods. Firstly, general change of hip was evaluated using Bath AS radiology hip index (BASRI-h). Radiographic hip involvement was defined as BASRI-h ≥ 2 [19]. Then, space width of hip was assessed using a published method, which measured the average inter-bone distance between acetabulum and femoral head at three distinct sites [1]. Assessments of X-ray were performed by an experienced rheumatologist who has been trained in musculoskeletal radiology. He was blinded to all clinical and other imaging data.

Magnetic resonance image

MRI examinations were conducted at baseline and week 24 as well. MRI was obtained on a 1.5-T magnetic resonance imager (Achieva, Nova-Dual Philips medical systems, Netherlands) with 16-channel torso phase-array coil. Coronal and axial scanning was conducted for all patients. Six standard sequences MR imaging were performed: (1) axial T1-weighted turbo spin echo pre-gadolinium [repetition time (TR)/echo time (TE), 491 ms/10 ms]; (2) axial T2-weighted turbo spin echo (TR/TE, 4819 ms/100 ms); (3) axial spectral presaturation attenuated inversion recovery (TR/TE, 2495.5 ms/80 ms); (4) coronal spectral presaturation with

inversion recovery (TR/TE, 3925.7 ms/100 ms); (5) axial fat-saturated contrast-enhanced T1 turbo spin echo [TR/TE, 692.6 ms/10 ms; gadopentetate dimeglumine injection (15 ml:7.04 g), 0.2 ml/kg, at a rate of 1.5 ml/s]; and (6) coronal fat-saturated contrast-enhanced T1 turbo spin echo (TR/TE, 512.6 ms/18 ms). The axial imaging parameters were field of view (FOV) 320~330 mm × 280~300 mm, slice thickness 4.0 mm, and slice gap 0.5 mm. The coronal imaging parameters were FOV 320~330 mm × 380~390 mm, slice thickness 3.0 mm, and slice gap 0.5 mm.

We used the definition of hip changes in MRI examination, which has been described by Huang et al. [2]. Briefly, joint effusion and abnormal synovial enhancement are considered to be raised by synovitis. Furthermore, synovitis, enthesitis, and subchondral bone marrow edema are markers of acute inflammatory changes on hip MRI. Besides, subchondral erosive destruction, joint space narrowing, and ankylosis are signs of chronic inflammatory changes. MRI was read by an experienced radiologist who was blinded to clinical and the other imaging information.

Statistical analysis

Sample size calculation was performed for BASDAI using an equivalence design. An α level of 0.05 and β level of 0.1 (power of 90%) were used. Based on a previous study, BASDAI were estimated to be 1.42 ± 0.23 and 1.40 ± 0.35 in the tapering group and control group [8]. Prespecified equivalence margins for clinical significance of difference between groups were − 0.18 to 0.18. According to this calculation, at least 52 patients per group were required. Equivalence of groups was declared if the 95% confidence interval (CI) for the mean difference of BASDAI was included between the prespecified margins.

Categorical data between groups or visits was compared through χ^2 test, χ^2 test with continuity correction, or Fisher's exact test when appropriate. Continuous data with normal distribution was compared using t test. Mann-Whitney U test was used to evaluate continuous data with non-normal distribution. A linear mixed model (LMM) with an unstructured covariance matrix and a restricted maximum likelihood estimate was used to evaluate differences over time in longitudinal parameters between groups. Clinical parameters were modeled with fixed effects of tapering group (with control group as reference), baseline (with week 24 as reference) and week 12 (with week 24 as reference), and interaction (tapering group × baseline and tapering group × week 12), with a random intercept. Regarding radiologic data, models included tapering group (with control group as reference), baseline (with week 24 as reference), and interaction (tapering group × baseline) as fixed effect, with a random intercept.

Data analysis and management were performed using SPSS 18.0. $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

Of 136 AS patients being retrospectively evaluated in this study, 80 of them were in the tapering group, while the others received full-dose therapy until week 24. There was no significant difference in demographic and clinical characteristics between groups at baseline (Table 1, $p > 0.05$). Besides, majority of patients suffered from long-standing AS with early onset disease. In terms of clinical manifestation, more than half of patients had hip arthritis, because of high prevalence of hip pain and positive rate of the Patrick's test. Finally, disease activities of AS patients were high, due to the elevation of BASDAI, ASDAS-CRP, and acute phase reactants.

Cumulatively, each patient of tapering group received 18 Yisaipu® treatments, while the others undertook 24 subcutaneous injections. Regarding the background therapy, medium (interquartile range) of 24-week MPRs in the tapering group was 97% (8%), which was similar to that of the control group (95% (8%), $p > 0.05$). Besides, 24-week MPRs of all patients were greater than 80%, which indicated their good adherence to celecoxib.

Clinical assessment

The estimated difference between the tapering group and control group in mean BASDAI was 0.04, and 95% CI (− 0.06 to 0.14) was entirely included between prespecified margins (− 0.18 to 0.18). This result demonstrated the clinical equivalence between groups in general.

LMM exhibited that main effects of tapering group with control group as reference in BASDAI, ASDAS-CRP, CRP, ESR, and BASFI were not significant (Table 2, $p > 0.05$). Besides, main effects of baseline with week 24 as reference reached statistically significant ($p < 0.05$), while main effects of week 12 with week 24 as reference were insignificant ($p > 0.05$). Interactions were not significant in these parameters ($p > 0.05$). These results indicated that efficacy of Yisaipu® dose reduction and full-dose treatment was similar. After achieving low disease activity or remission in week 12, patients in both groups kept general disease activity stable until week 24. Their disease activity parameters in week 24 were still lower than those of baseline.

Table 3 displays no significant main effect in VAS of bilateral hip pain levels and HHS between groups ($p > 0.05$). In addition, main effects of baseline with week 24 as reference were significant ($p < 0.05$), while those of week 12 with week 24 as reference were not ($p > 0.05$). Interactions did not reach

Table 1 Demographic and clinical characteristics of ankylosing spondylitis patients at baseline

Parameters	Tapering group ($n = 80$)	Control group ($n = 56$)	p value
Male gender, *n* (%)	67 (83.75)	50 (89.29)	0.36
Age (years), median (IQR)	26.00 (9.00)	28.50 (9.75)	0.92
Disease duration (years), median (IQR)	7.00 (6.00)	7.50 (5.25)	0.10
Hip pain, *n* (%)	56 (70.00)	37 (66.07)	0.63
Involvement of peripheral joint (s), *n* (%)	32 (40.00)	21 (37.50)	0.77
Uveitis, *n* (%)	7 (8.75)	3 (5.36)	0.68[a]
IBD, *n* (%)	2 (2.50)	1 (1.25)	1.00[b]
Psoriasis, *n* (%)	2 (2.50)	2 (3.57)	1.00[b]
Enthesitis, *n* (%)	9 (11.25)	6 (10.71)	0.92
Dactylitis, *n* (%)	2 (2.50)	1 (1.25)	1.00[b]
Positive of HLA-B27, *n* (%)	64 (80.00)	47 (83.93)	0.56
Family history of AS, *n* (%)	17 (21.25)	12 (21.42)	0.98
Positive of Patrick's test, *n* (%)	45 (56.25)	29 (51.79)	0.61
CRP (mg/L), mean ± SD	23.90 ± 13.42	22.91 ± 10.77	0.65
ESR (mm/h), mean ± SD	41.13 ± 22.19	38.69 ± 21.97	0.53
ASDAS-CRP, mean ± SD	3.78 ± 0.64	3.77 ± 0.56	0.93
BASDAI, mean ± SD	5.26 ± 0.91	5.19 ± 0.94	0.64
BASFI, mean ± SD	3.80 ± 1.22	3.57 ± 1.10	0.26
VAS	3.96 ± 1.19	3.95 ± 1.57	0.90
HHS, mean ± SD	51.51 ± 10.11	50.89 ± 9.29	0.95

IQR interquartile range, *IBD* inflammatory bowel disease, *HLA-B27* human leukocyte antigen-B27, *AS* ankylosing spondylitis, *CRP* C-reactive protein, *SD* standard deviation, *ESR* erythrocyte sedimentation rate, *ASDAS-CRP* ankylosing spondylitis disease activity score-C-reactive protein, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *VAS* bilateral hip pain levels on a visual analogue scale, *HHS* Harris hip score

[a] χ^2 test with continuity correction was performed

[b] Fisher's exact test was performed

statistically significant ($p > 0.05$). These results suggested that this etanercept-biosimilar tapering therapy maintained local symptom and function stable in the last 12 weeks, and both parameters were better in week 24 comparing with those of baseline. Their efficacy on local symptom and function was comparable to the conventional therapy.

X-ray assessment

Every hip was evaluated separately, so 272 hips were assessed. BASRI-h of 71 (44.34%) hips in patients from the tapering group and 51 (45.54%) hips from the control group was equal or greater than 2 at baseline. χ^2 test showed that prevalence of radiological hip involvement was similar between groups ($p > 0.05$).

LMM revealed main effects of tapering group with control group as reference and baseline with week 24 as reference, and interaction (tapering group × baseline) did not reach statistically significant (Table 4, $p > 0.05$).

Space width of hips in the tapering group and control group was 3.02 ± 0.84 mm and 3.07 ± 0.77 mm at baseline ($p > 0.05$), respectively. Twenty-four weeks later, these distances were 3.03 ± 0.83 mm and 3.12 ± 0.72 mm. Main effects of tapering group and baseline, and interaction (tapering group × baseline) were insignificant ($p > 0.05$).

Magnetic resonance imaging assessment

One hundred and twenty-five (78.12%) and 88 (78.57%) hips in the tapering group and control group were detected positive changes in MRI examination at baseline ($p > 0.05$). LMM showed that main effects of baseline with week 24 as reference in all acute inflammatory changes were significant ($p < 0.05$). Main effects of tapering group with control group as reference and interaction (tapering group × baseline) were not (Table 5, $p > 0.05$). These results indicated that dose reduction therapy of this etanercept-biosimilar kept improvement of acute inflammation in hip, which was comparable to full-dose of this etanercept-biosimilar. Representative positive MRI changes of active inflammation are depicted in Fig. 1.

Regarding chronic inflammatory changes, main effects of tapering group and baseline, interaction (tapering group × baseline) were not significant in general ($p > 0.05$). However, main effect of tapering group with control group

Table 2 Linear mixed model of systemic disease activity and function of the tapering group ($n = 80$) and control group ($n = 56$)

Dependent variables	Groups	Visits			Parameters	Tapering group[a]	Baseline[b]	Week 12[b]	Tapering group × baseline[c]	Tapering group × week 12[c]
		Baseline	Week 12	Week 24						
BASDAI, mean ± SD	Tapering group	5.26 ± 0.91	1.21 ± 0.38	1.18 ± 0.30	PE (SE)	0.04 (0.10)	1.13 (0.41)	0.05 (0.93)	0.03 (0.15)	− 0.03 (0.15)
	Control group	5.19 ± 0.94	1.19 ± 0.33	1.14 ± 0.28	*p* value	0.68	< 0.001	0.95	0.83	0.86
ASDAS-CRP, mean ± SD	Tapering group	3.78 ± 0.64	1.00 ± 0.55	1.09 ± 0.52	PE (SE)	0.16 (0.10)	2.84 (0.10)	0.08 (0.10)	− 0.15 (0.14)	− 0.16 (0.14)
	Control group	3.77 ± 0.56	1.01 ± 0.50	0.93 ± 0.50	*p* value	0.10	< 0.001	0.47	0.28	0.24
CRP (mg/L), mean ± SD	Tapering group	23.90 ± 13.42	10.11 ± 8.26	10.17 ± 9.34	PE (SE)	2.09 (1.70)	14.83 (1.84)	1.96 (1.84)	− 1.10 (2.40)	− 2.03 (2.40)
	Control group	22.91 ± 10.77	10.05 ± 7.51	8.08 ± 6.45	*p* value	0.22	< 0.001	0.29	0.65	0.40
ESR (mm/h), mean ± SD	Tapering group	41.13 ± 22.19	17.25 ± 16.65	17.96 ± 17.59	PE (SE)	2.67 (3.22)	23.40 (3.49)	1.91 (3.49)	− 0.23 (4.55)	− 2.61 (4.55)
	Control group	38.69 ± 21.97	17.20 ± 15.47	15.29 ± 14.97	*p* value	0.41	< 0.001	0.59	0.96	0.57
BASFI, mean ± SD	Tapering group	3.80 ± 1.22	1.25 ± 0.78	1.42 ± 0.86	PE (SE)	0.23 (0.17)	2.38 (0.18)	0.14 (0.37)	− 0.01 (0.23)	− 0.31 (0.23)
	Control group	3.57 ± 1.10	1.33 ± 0.74	1.19 ± 0.86	*p* value	0.16	< 0.001	0.70	1.00	0.19

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *SD* standard deviation, *PE* (unstandardized) parameter estimate, *SE* standard error, *ASDAS-CRP* ankylosing spondylitis disease activity score-C-reactive protein, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *BASFI* Bath Ankylosing Spondylitis Functional Index

[a] Reference group: control group

[b] Reference group: week 24

[c] Reference group: control group × week 24

as reference in fat accumulation nearly reached statistically significant ($p = 0.08$). These results were comparable to X-ray examination, which showed no significant change of hip structure in both groups during 24 weeks.

Discussion

Hip arthritis is crucial for AS patients, since it increases the burden of disease and causes a reduction in physical function [4]. However, prevalence of hip arthritis in patients with AS is still uncertain, since its definition is controversial, including X-ray, MRI, clinical manifestation, and hip replacement [2, 20]. That was the reason why AS patients with high disease activity were enrolled in this study, rather than concerning the criteria of hip arthritis for AS patients.

TNFi is a promising therapy for hip arthritis in patients with AS [20]. For instance, Wang et al. [21] showed that etanercept relieved hip pain and improved its function. Besides, TNFi might reduce the need for hip replacement and alter the prognosis of AS, as a result of alleviating hip arthritis [6]. Nevertheless, data on efficacy of TNFi dose reduction for hip arthritis in AS patients remains limited, so this retrospective study was performed. We suggested that Yisaipu® dose reduction decreased disease activity and improved acute inflammation in MRI examination. Besides, efficacy of this etanercept-biosimilar tapering was equivalent to full-dose therapy, based on similar background characteristics and therapy.

Dose reduction of TNFi is able to maintain low disease activity and clinical remission. As an illustration, Arends et al. [22] revealed patient-tailored tapering of TNFi preserving low disease activity over 2 years, by observing 58 patients with AS. In addition, 60%-dose infliximab could successfully sustain the treatment effect [23]. Based on our clinical equivalence analysis, efficacy of Yisaipu® tapering therapy was similar to standard therapy. 95% CI of estimated difference was fully included between a widely accepted equivalence margin of 80 to 125% as well [24]. Furthermore, this etanercept-biosimilar tapering kept systemic disease activity low by monitoring ASDAS-CRP and acute phase reactants.

This study contained a group of longitudinal data, and various methods have been developed for analyzing this sort of data. LMM was used to examine the efficacy between Yisaipu® tapering and conventional therapy, because this model could directly answer question of interest [25]. Demographic background and clinical characteristics were similar between patients who received dose reduction and standard etanercept-biosimilar therapy, and this was a monocentric study. So, we considered that lack of usual potential confounder was in our study, and group, visit, and interaction (group × visit) were chosen as the fixed effect of LMM analysis. Due to the nature of LMM, *p* value has not

Table 3 Linear mixed model of hip arthritis assessment in the tapering group ($n = 80$) and control group ($n = 56$)

Dependent variables	Groups	Visits			Parameters	Tapering group[a]	Baseline[b]	Week 12[b]	Tapering group × baseline[c]	Tapering group × week 12[c]
		Baseline	Week 12	Week 24						
VAS, mean ± SD	Tapering group	3.96 ± 1.19	1.09 ± 0.84	1.19 ± 1.06	PE (SE)	0.26 (0.19)	3.02 (0.20)	0.05 (0.20)	− 0.24 (0.26)	− 0.15 (0.26)
	Control group	3.95 ± 1.57	0.98 ± 0.84	0.93 ± 0.71	*p* value	0.16	< 0.001	1.00	0.36	0.56
HHS, mean ± SD	Tapering group	51.51 ± 10.11	76.31 ± 9.96	75.99 ± 8.93	PE (SE)	− 0.17 (1.14)	− 25.26 (8.12)	− 2.11 (6.67)	0.79 (1.61)	2.43 (1.61)
	Control group	50.89 ± 9.29	74.05 ± 8.80	76.16 ± 7.74	*p* value	0.88	0.002	0.75	0.62	0.13

VAS bilateral hip pain levels on a visual analogue scale, *SD* standard deviation, *PE* (unstandardized) parameter estimate, *SE* standard error, *HHS* Harris hip score

[a] Reference group: control group

[b] Reference group: week 24

[c] Reference group: control group × week 24

been adjusted. We found that efficacy of both treatments was comparable on the general disease activity, and patients kept remission or low disease activity from week 12 to week 24.

Several clinical parameters are able to be used to assess general disease activity and function of AS patients, such as ASDAS-CRP, BASDAI, and BASFI, which were validated in Chinese population [26, 27]. However, few studies focus on change of hip arthritis in AS patients because of insufficient clinical scales for this joint. Despite VAS of bilateral hip pain and HHS that have not been validated in China, they were chosen for this study, since they had been widely used as outcome measures for individuals with hip diseases [28, 29]. Our study revealed that these parameters of tapering group kept stable in the last 12 weeks, which were consistent with those of the control group. Correspondingly, Lian et al. [9] demonstrated that etanercept dose reduction adequately maintained stable HHS for 6 months. Our finding is also consistent with that of Li et al. [8], who showed that clinical remission of hip synovitis in AS patients was maintainable.

Regarding change of hip in AS patients who undergo TNFi treatment, studies of X-ray are still rare. Interestingly, BASRI-h slightly decreased from 3 to 2 in a case series of TNFi therapy, which only included six AS patients [30]. Konsta et al. [31] demonstrated that the absence of radiographic progression of hip arthritis was in 23 AS patients, because BASRI-h merely kept constant during infliximab therapy. In agreement with this study, our result showed that BASRI-h nearly unchanged in both groups, which elucidated that the effect of preventing radiographic progression of hip arthritis is similar between etanercept-biosimilar tapering and full-dose therapy.

Space width of hip is the other radiological parameter which closely associated to severity of hip arthritis and functional impairment in AS patients [1, 31]. Studies reported that TNFi therapy increased space width [1, 31, 32]. Unlike these previous reports, limited change was detected in our study, even in the patients who underwent conventional etanercept-biosimilar treatment. This might partially relate to the relatively short observation time.

Table 4 Change of Bath Ankylosing Spondylitis Radiology Index for 272 hips from 136 patients

Grade	Tapering group ($n = 160$)		Control group ($n = 112$)	
	Baseline	Week 24	Baseline	Week 24
0, *n* (%)	40 (25.00)	39 (24.34)	28 (25.00)	28 (25.00)
1, *n* (%)	49 (30.63)	48 (30.00)	33 (29.46)	33 (29.46)
2, *n* (%)	44 (27.50)	46 (28.75)	34 (30.36)	34 (30.36)
3, *n* (%)	24 (15.00)	24 (15.00)	15 (13.39)	15 (13.39)
4, *n* (%)	3 (1.88)	3 (1.88)	2 (1.78)	2 (1.78)

Table 5 Linear mixed model of magnetic resonance imaging analysis for tapering group ($n = 160$) and control group ($n = 112$)

MRI features	Groups	Visits		Parameters	Tapering group[a]	Baseline[b]	Tapering group × baseline[c]
		Baseline	Week 24				
Joint effusion, *n* (%)	Tapering group	110 (68.75)	28 (17.50)	PE (SE)	0.02 (0.05)	0.54 (0.06)	− 0.02 (0.07)
	Control group	75 (66.96)	16 (14.29)	*p* value	0.66	< 0.001	0.75
Abnormal synovial enhancement, *n* (%)	Tapering group	119 (74.38)	30 (18.75)	PE (SE)	0.02 (0.05)	0.58 (0.06)	− 0.02 (0.07)
	Control group	84 (75.00)	19 (16.96)	*p* value	0.73	< 0.001	0.74
Synovitis, *n* (%)	Tapering group	120 (75.00)	31 (19.38)	PE (SE)	0.02 (0.05)	0.58 (0.55)	− 0.02 (0.07)
	Control group	85 (75.89)	20 (17.86)	*p* value	0.77	< 0.001	0.74
Bone marrow edema, *n* (%)	Tapering group	28 (17.50)	9 (5.63)	PE (SE)	0.01 (0.04)	0.13 (0.04)	− 0.01 (0.05)
	Control group	19 (16.96)	5 (4.46)	*p* value	0.76	< 0.001	0.91
Enthesitis, *n* (%)	Tapering group	59 (36.88)	6 (3.75)	PE (SE)	− 0.01 (0.05)	0.33 (0.05)	0.00 (0.06)
	Control group	42 (37.50)	5 (4.46)	*p* value	0.88	< 0.001	0.99
Active inflammatory changes, *n* (%)	Tapering group	123 (76.88)	32 (20.00)	PE (SE)	0.00 (0.05)	0.57 (0.06)	0.00 (0.07)
	Control group	86 (76.79)	22 (19.64)	*p* value	0.94	< 0.001	0.97
Bone erosion, *n* (%)	Tapering group	36 (22.50)	37 (23.13)	PE (SE)	0.00 (0.05)	0.00 (0.06)	0.00 (0.07)
	Control group	26 (23.21)	26 (23.21)	*p* value	0.99	1.00	0.93
Fat accumulation, *n* (%)	Tapering group	20 (12.50)	28 (17.50)	PE (SE)	− 0.08 (0.05)	− 0.06 (0.05)	0.01 (0.07)
	Control group	16 (14.29)	23 (20.54)	*p* value	0.08	0.22	0.85
Ankylosis, *n* (%)	Tapering group	7 (4.38)	7 (4.38)	PE (SE)	0.00 (0.03)	− 0.04 (0.03)	0.00 (0.04)
	Control group	5 (4.46)	5 (4.46)	*p* value	0.95	0.18	0.98
Chronic inflammatory changes, *n* (%)	Tapering group	40 (25.00)	48 (30.00)	PE (SE)	0.02 (0.05)	− 0.02 (0.06)	− 0.03 (0.08)
	Control group	29 (25.89)	31 (27.69)	*p* value	0.67	0.77	0.68

MRI magnetic resonance image, *PE* (unstandardized) parameter estimate, *SE* standard error

[a] Reference group: control group

[b] Reference group: week 24

[c] Reference group: control group × week 24

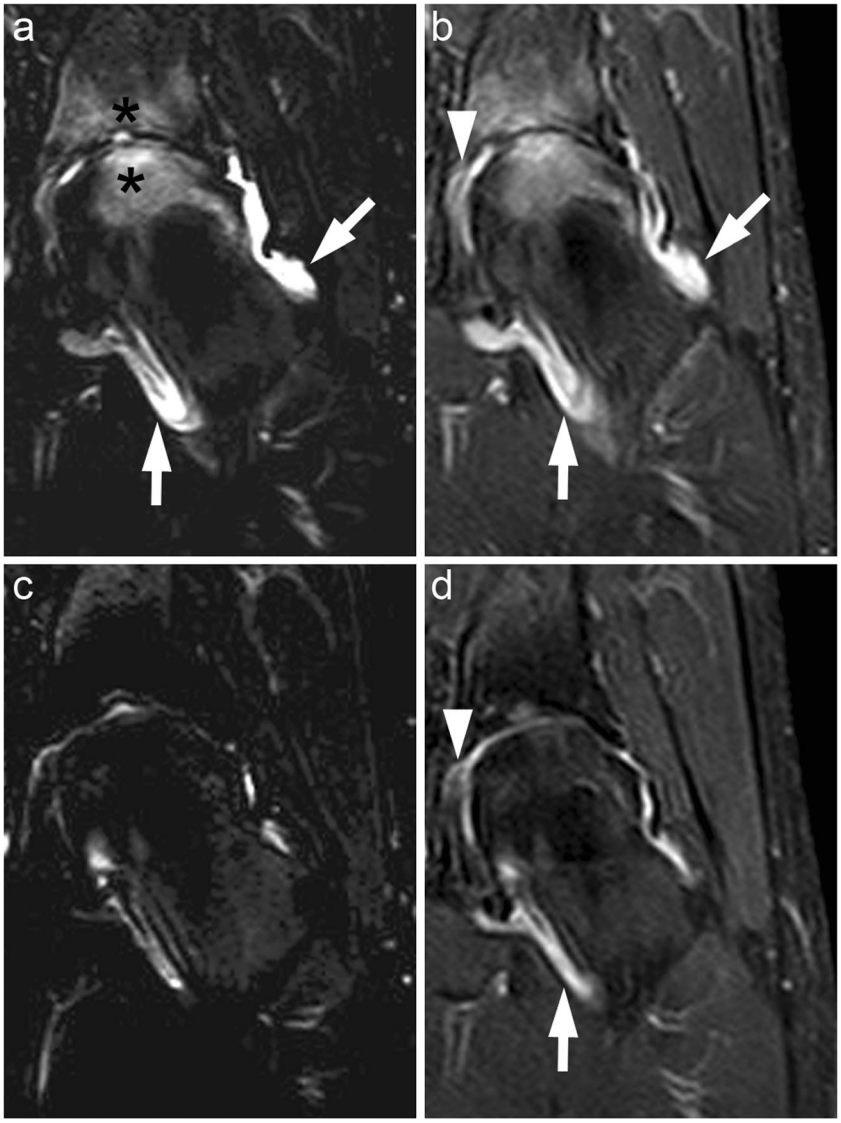

Fig. 1 Magnetic resonance imaging of left hip in an ankylosing spondylitis patient before (**a**, **b**) and after (**c**, **d**) Yisaipu® tapering therapy. **a** Coronal spectral presaturation with inversion recovery showed joint effusion (arrows) and bone marrow edema (asterisks). **b** Abnormal synovial enhancement (arrows) and enthesitis (arrowhead) were displayed in coronal fat-saturated contrast-enhanced T1 turbo spin echo at the same slice. **c** Significant reduction of joint effusion and bone marrow edema was detected at week 24. **d** Abnormal synovial enhancement (arrow) and enthesitis (arrowhead) were still existed, but they considerably improved

MRI is a helpful imaging tool for displaying acute and chronic musculoskeletal lesions in AS patients [33]. Since variety of sequences are available in MRI examination, it can be used to assess different kinds of lesions in hip [34]. Additionally, onset of hip arthritis may be concealed in AS patients, so it is uneasy to be diagnosed according to history and physical examination. Once definitive involvement of hip can be detected by plain X-ray examination, hip arthritis has progressed to a late-stage. In order to discover hip arthritis in early-stage, MRI examination is necessary, because it precisely depicts acute inflammatory lesions [35]. In our study, nearly 80% hips were abnormal in MRI examination, which was about twice of hip arthritis being detected by X-ray.

MRI is sensitive to acute inflammatory change, so this imaging tool is used to monitor disease activity in rheumatic diseases [36]. This is exemplified in Althoff et al.'s report [37], which shows that etanercept improved enthesitis in patients with early axial spondyloarthritis, using whole body MRI examination. In addition, adalimumab decreases BASDAI, BASFI, and sacroiliac joint MRI score in parallel [38]. Regarding hip arthritis of AS patients, MRI score system was scarce until now. To the best of our knowledge, Huang et al. [2] presented a binary method, which included comprehensive characteristics of hip arthritis, so it was chosen for this study. We found that acute inflammatory changes significantly improved in patients either received dose reduction or full-dose therapy. Furthermore, efficacy of etanercept-biosimilar tapering therapy was comparable to the standard dose treatment. This result was similar to a previous study, which showed etanercept tapering treatment suppressed synovitis and reduced joint effusion [9].

Unlike acute inflammatory changes, the chronic inflammation nearly unchanged during treatment in both groups. This result was coincident with a previous study, which revealed TNFi inhibited progression of hip arthritis in AS patients [32]. It was worth to note that prevalence of fat

accumulation increased in both groups, especially in the control group, though differences did not reach statistically significant comparing with baseline. Chiowchanwisawakit et al. [39] indicated fat accumulation related to new bone formation in spine and sacroiliac joint of AS patients, and this feature was likely to reflect previous inflammation. However, significance of fat accumulation in hip arthritis of AS patients is still uncertain.

This study has some limitations which were needed to be addressed. The main limitation of this study was a monocentric study with retrospective nature, though data has been collected prospectively. To our knowledge, there is no prospective multicentric study which concerned the effect of TNFi on hip arthritis of AS patients. Second, we chose BASDAI for sample size calculation, because of no available data regarding difference of hip abnormality between tapering and full-dose TNFi therapy in AS patient. We found clinical equivalence between these treatments in general, after reviewing 136 AS patients. The sample size of our study is relatively larger, comparing with the previous reports [8, 9]. Third, the follow-up period of our study was short. Since TNFi has the advantage of rapid onset and high efficacy [40], we decided that patients undertook full-dose TNFi therapy for only 12 weeks. Besides, a previous study observed AS patients who took etanercept tapering treatment for 8 weeks, after they received full-dose therapy for 4 weeks. This study provided a hopeful result, which demonstrated etanercept dose reduction maintained hip arthritis remission [8]. Our follow-up length was longer than this study.

In conclusion, this study suggests that Yisaipu® tapering therapy shares equivalent clinical efficacy on disease activity and function of hip in AS patients, comparing with those of conventional treatment. MRI study probably showed that this etanercept-biosimilar dose reduction improved acute inflammatory changes. Its efficacy is comparable to the standard therapy. Further prospective studies are needed to verify our results.

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Compliance with ethical standards

This study was approved by the ethics committee of Guangdong second provincial general hospital (2015-KLYY-0015). Written informed consents in accordance with the declaration of Helsinki were given by participants.

Disclosures None.

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