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ORIGINAL ARTICLE

Effective serum level of etanercept biosimilar and effect of antidrug antibodies on drug levels and clinical efficacy in Chinese patients with ankylosing spondylitis

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Abstract

Objectives To investigate the effective serum level of etanercept biosimilar in Chinese patients with ankylosing spondylitis (AS) who achieve AS Disease Activity Score-C-reactive protein (ASDAS-CRP) < 2.1, and the effect of antidrug antibodies on drug levels and clinical efficacy.

Methods Our study enrolled 60 patients with AS who were treated with etanercept biosimilar. Serum and clinical data were collected at baseline and treatment weeks 4, 12, and 24. Drug levels and antidrug antibody levels were measured using an enzyme-linked immunosorbent assay while tumour necrosis factor (TNF)-α levels were measured using cytometric bead array. A receiver operating characteristic (ROC) curve was used to analyse effective serum level of etanercept biosimilar.

Results Patients with ASDAS-CRP ≥ 2.1 exhibited significantly lower drug levels than those with ASDAS-CRP < 2.1 did. The cut-off values of effective serum level of patients with AS who achieved ASDAS-CRP < 2.1 at weeks 4, 12, and 24 were 2.32, 2.12, and 2.36 μg/mL, respectively. Patients with drug levels above the cut-off value had lower Bath AS Disease Activity Index (BASDAI) and TNF-α levels. Antidrug antibodies had no effect on the Assessment of Spondylosis Arthritis International Society (ASAS) remission rates, but patients with antidrug antibodies had lower drug levels and higher TNF-α levels.

Conclusions Detecting serum drug levels and antidrug antibody levels might facilitate estimation of the clinical efficacy and adjustment of medication regimen during etanercept biosimilar therapy in Chinese patients with AS.

Keywords Ankylosing spondylitis · Biological therapy · Drug monitoring · Etanercept · Pharmacokinetics

Introduction

Etanercept, a fusion protein of tumour necrosis factor (TNF)-α inhibitor, has been approved for the treatment of active ankylosing spondylitis (AS) that is unresponsive to routine treatment. Numerous clinical studies have shown that most patients tolerated etanercept well, which could effectively improve the clinical symptoms of AS [1–3]. As a matter of fact, biosimilars of etanercept used in the treatment of AS have been produced constantly in recent years and it is very important to evaluate their clinical efficacy. As a biosimilar of etanercept, yisaipu (YSP) has been used in China for 13 years and has shown no significant difference in clinical efficacy and safety compared to etanercept [4–6]. Presently, the YSP is not only used in China, but is used in other Asian countries such as India, Bangladesh, and Cambodia, as well as North America and South America.

Recent studies have shown that low-dose etanercept also effectively reduces the disease activity in patients with AS [7, 8]. A study of 162 patients with AS who were treated with etanercept 50 mg subcutaneously weekly showed that lower etanercept levels were associated with high disease activity [9]. Another study of 192 patients showed that patients who were unresponsive to etanercept exhibited lower etanercept levels than those who responded did [10]. Although Kneepkens et al. [9] opined that measuring etanercept levels might facilitate the identification of over- or undertreatment and, thereby, optimise etanercept therapy in AS, they did not

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suggest an effective cut-off value of etanercept level. However, the relationship between the YSP level and disease activity, as well as the effective level of YSP which determines whether a Chinese patient with AS, could achieve ASDAS-CRP < 2.1 has not yet been reported in any study.

Approximately 20–40% of patients were unresponsive to TNF-inhibitor treatment or their clinical symptoms relapsed during subsequent treatment [11]. The immunogenicity of biologics exposes patients treated with infliximab and adalimumab to the possibility of developing antidrug antibodies (ADA) against the administered biologics [12, 13], which were associated with low drug levels and poor clinical efficacy [14]. Up to 18% of patients have been shown to produce anti-etanercept antibodies, which have no effect on the Assessment of Spondylosis Arthritis International Society (ASAS) remission rates [15, 16]. However, whether ADA affects the YSP level and clinical efficacy is still unknown.

Therefore, this study was designed to investigate the relationship between the YSP level and disease activity, and the cut-off values of effective YSP level, as well as the effect of the ADA on YSP levels and clinical efficacy in Chinese patients with AS to provide a basis for medication optimisation and guidance for precise treatments.

Patients and methods

Patients

Sixty patients with AS (54 male and 6 female patients with an average age of 29.50 ± 6.97 and 30.20 ± 7.57 years, respectively) who received YSP therapy at the Department of Rheumatology and Immunology of China-Japan Union Hospital of Jilin University were enrolled in this study.

All the patients were diagnosed according to the 1984 modified New York Criteria for AS [17] and were in an active disease (Bath AS Disease Activity Index, BASDAI ≥ 4, night back pain ≥ 4 [18]) at baseline. They had used at least one non-steroidal anti-inflammatory drug (NSAID) for more than 4 weeks but experienced poor efficacy or intolerance. None of the patients had used any biologicals, steroids, or disease-modifying anti-rheumatic drugs (DMARDs) for more than 4 weeks before starting of the YSP treatment according to the International ASAS consensus statement for the use of anti-TNF agents in patients with AS [19]. None of the patients had complications such as infectious diseases, tuberculosis, tumours, and hematologic or other systemic diseases.

Additionally, 21 matched healthy individuals (18 male and 3 female individuals with an average age of 29.30 ± 7.61 and 31.60 ± 9.31 years, respectively) were recruited from the Medical Examination Center of the China-Japan Union Hospital of Jilin University as the healthy control group. They had not used any biologicals, or had any history of rheumatic diseases. The basic characteristics of the patients and healthy controls are shown in Table 1.

Study design

The patients were administered YSP (recombinant human TNF-α receptor II: immunoglobulin (IgG) Fc fusion protein for injection, Sunshine Guojian Pharmaceutical, Shanghai Co., Ltd., China) 50 mg subcutaneously injection weekly, and their serum and clinical data were collected at baseline and weeks 4, 12, and 24 of treatment. The clinical characteristics included BASDAI, Bath AS Functional Index (BASFI), Bath AS Measurement Index (BASMI), AS Disease Activity Score-C-reactive protein (ASDAS-CRP), CRP, erythrocyte sedimentation rate (ESR), YSP level, ADA level, and TNF-α level. The serum samples were stored at − 80 °C until analysed.

This study was conducted in accordance with the ethical standards of the Helsinki Declaration and approved by the Ethical Committee of the China-Japan Union Hospital of Jilin University (approval number, 2015-wjw008). Each patient was selected following a rigorous process and provided written informed consent to participate.

Therapeutic responsiveness

The patients were evaluated with ASAS 20, ASAS 40, ASAS partial remission, or ASAS 5/6 based on their disease activity at each interval according to the ASAS handbook [20]. In addition, inactive or moderate disease was defined as ASDAS-CRP < 2.1 [21].

Measurement methods

BASDAI and BASFI were measured using the visual analogue score (VAS); ASDAS-CRP was calculated using BASDAI, patient global assessment (PGA), and CRP values [21]; and BASMI was measured using a 3-point method [22]. ESR

Table 1 Basic characteristics of ankylosing spondylitis patients and healthy control subjects

	Patients	Healthy control	*p*
n	60	21	–
Age (years)	29.55 ± 6.96	31.80 ± 10.53	NS
Height (cm)	170.67 ± 7.95	170.24 ± 6.43	NS
Weight (kg)	67.04 ± 13.24	66.90 ± 10.04	NS
BMI (kg/m^2)	22.96 ± 3.93	22.99 ± 2.38	NS
Disease duration (years)	4.00 (1.10–8.00)	–	–
TNF-α (pg/mL)	35.96 ± 7.35	7.21 ± 0.36	< 0.001

Mean ± standard deviation (SD) and median (interquartile range, IQR) are shown

BMI, body mass index; *TNF*, tumour necrosis factor; *NS*, not significant

(mm/h) and CRP (mg/L) were detected using the Westergren method and the Raten nephelometry method, respectively.

The YSP (μg/mL) and ADA (ng/mL) levels were measured using ELISA kits designed by Theradiag Co., Ltd. (France), based on a specific double antibody sandwich method. The serum TNF-α levels (pg/mL) were measured using cytometric bead array (CBA). The CBA kits were purchased from Becton Dickinson Medical Devices Co., Ltd. in Shanghai, China.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software V. 18.0 was used for the statistical analysis. All data were analysed to determine the normality of distribution using the Shapiro-Wilk test.

The repeated measures analysis of variance (ANOVA) and Friedman test were used to determine whether there were changes in variables over time for normal distribution and abnormal distribution values, respectively. For comparison of variables of patients divided into two groups, independent-sample *t* test was used for normal distribution variables, whereas the Wilcoxon rank-sum test was used for abnormal variables. Pearson and Spearman rank correlation analyses were used to analyse the correlation between the YSP levels and improvement of the clinical data, for normal distribution and abnormal distribution values, respectively. A receiver operating characteristic (ROC) curve was used to analyse the cut-off value, sensitivity, and specificity of effective YSP levels at each interval. Chi-square test was used to compare the ASAS remission rates between two groups. Differences were considered significant when $p < 0.05$.

Results

Clinical data, YSP levels, and TNF-α levels of patients at each interval

The TNF-α level of patients with AS was significantly higher than that of the healthy controls at baseline ($p < 0.001$), while no significant difference occurred in the other characteristics between both groups (Table 1).

Fifty-five patients (91.67%) achieved at least ASAS 20 remission at treatment week 12, and only one patient (1.67%) did not achieve ASAS remission at the end of the treatment. Clinical data as well as the YSP and TNF-α levels of patients with AS at baseline and weeks 4, 12, and 24 of treatment are shown in Table 2.

After 24 weeks of the YSP treatment, the clinical data were significantly improved compared to those at baseline. We found that the YSP level increased significantly from 0 μg/mL at baseline to an average of 2.24 ± 1.32 μg/mL ($p < 0.001$) at week 4 while the levels at week 12 and 24 did not increase further ($p > 0.05$). At week 24, the TNF-α level of the patients was reduced significantly compared with that at baseline ($p < 0.001$) but was still higher than that of the healthy controls ($p = 0.044$).

Correlation between the YSP levels and improvement in clinical data

The correlations between the YSP levels and improvement in the clinical data at each interval compared to baseline are shown in Table 3.

We found no significant correlation between the YSP level and an improvement in clinical data at week 4. Furthermore, the YSP level was significantly correlated with improvement of the BASDAI at week 12, and improvement of the BASDAI, ASDAS-CRP, and CRP at week 24. These results suggest higher YSP levels are associated with greater improvement in clinical data.

Cut-off values of the YSP level at each interval

Patients were divided into two groups according to whether they achieved ASDAS-CRP < 2.1 at each interval. We found that the YSP levels were significantly higher in patients with ASDAS-CRP < 2.1 (2.56 ± 1.31, 2.43 ± 1.17, and 2.64 ± 1.22 μg/mL at week 4, 12, 24, respectively) than in patients with ASDAS–CRP ≥ 2.1 (1.51 ± 0.63, 1.61 ± 0.26, and 1.66 ± 1.05 μg/mL at weeks 4, 12, and 24, respectively, Fig. 1).

Then, we calculated the cut-off values of effective YSP levels when patients achieved ASDAS-CRP < 2.1 at each interval by ROC curve. The results showed that the cut-off values at weeks 4, 12, and 24 were 2.32, 2.12, and 2.36 μg/mL, respectively, while the sensitivity and specificity values were 53.7% and 94.4%, 60.8% and 86.7%, and 59.2% and 85.7%, respectively. In addition, the area under the curve (AUC) values were 0.758 ($p = 0.002$, 95% confidence interval (CI), 0.635–0.881), 0.709 ($p = 0.005$, 95% CI, 0.571–0.846), and 0.723 ($p = 0.008$, 95% CI, 0.503–0.916) at weeks 4, 12, and 24, respectively (Fig. 2a, b, c).

Furthermore, the patients were divided into two groups based on whether their the YSP levels reached the cut-off value at each interval. We found that compared with patients with the YSP levels below the cut-off value, those with levels above the cut-off value had lower BASDAI (2.12 ± 1.47 vs 2.91 ± 1.56, $p = 0.023$; 1.86 ± 1.11 vs 2.48 ± 1.46, $p = 0.036$; and 1.43 ± 1.05 vs 1.75 ± 1.30, $p = 0.158$ at weeks 4, 12, and 24, respectively) and TNF-α levels (21.61 ± 8.61 vs 29.07 ± 7.81 pg/mL, $p = 0.016$ and 9.54 ± 3.96 vs 14.17 ± 3.30 pg/mL, $p = 0.013$ at weeks 12 and 24, respectively, Fig. 2d, e). Although patients with the YSP levels above the cut-off value had higher TNF-α level than those below the cut-off value (31.03 ± 15.84 pg/mL vs 27.51 ± 14.95 pg/mL) at week 4, the difference was not statistically significant ($p = 0.550$). In addition, we found that patients with the YSP levels below the cut-off value had higher body mass index (BMI) values than those above the cut-off value (23.85 ± 4.14 vs 21.79 ± 3.35 kg/m^2, $p = 0.042$) at treatment week 4,

Table 2 Clinical data, YSP levels, and TNF-α levels of patients with ankylosing spondylitis at baseline and weeks 4, 12, and 24 of treatment

	Baseline	Week 4	Week 12	Week 24
BASDAI	5.73 ± 1.09	2.67 ± 1.54*	2.20 ± 1.35*	1.58 ± 1.18*,#,¶
BASFI	4.47 ± 2.35	2.29 ± 1.81*	1.78 ± 1.53*	1.16 ± 1.20*,#
BASMI	2.50 (1.00–4.00)	2.00 (1.00–3.00)$	1.50 (0.75–3.00)*	0 (0–1.00)*,#,§
ASDAS-CRP	3.77 ± 0.80	1.77 ± 0.63*	1.55 ± 0.52*	1.46 ± 0.61*,‡
ESR (mm/h)	25.32 ± 1.96	10.47 ± 2.00*	5.02 ± 1.29*,#	3.12 ± 1.89*,#
CRP (mg/L)	28.54 ± 8.30	4.39 ± 2.34*	4.08 ± 1.40*	4.45 ± 1.59*
YSP (μg/mL)	0	2.24 ± 1.32*	2.32 ± 1.20*	2.41 ± 1.29*
TNF-α (pg/mL)	35.96 ± 7.35	29.00 ± 5.30+	25.08 ± 3.65*	11.78 ± 3.20*,#,△

Mean ± standard deviation (SD) and median (interquartile range, IQR) are shown.

YSP, yisaipu; *TNF*, tumour necrosis factor; *BASDAI*, Bath Ankylosing Spondylitis Disease Activity Index; *BASFI*, Bath Ankylosing Spondylitis Functional Index; *BASMI*, Bath Ankylosing Spondylitis Measurement Index; *ASDAS-CRP*, Ankylosing Spondylitis Disease Activity Score-C-reactive protein; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein

*$p < 0.001$, $^{\$}p = 0.003$, $^{+}p = 0.009$ compared with baseline;

$^{\#}p < 0.001$, $^{\ddagger}p = 0.012$ compared with week 4;

$^{\triangle}p < 0.001$, $^{\P}p = 0.011$, $^{\S}p = 0.002$ compared with week 12

while there was no significant difference in BMI between the two groups at week 12 and 24.

ADA levels at each interval

We found that patients developed ADA at different intervals and some of patients who were ADA-positive reverted to a negative status following the treatment. ADA was undetectable at baseline. Furthermore, 18 (30%), 19 (31.7%), and 13 (21.7%) of patients were ADA-positive at weeks 4, 12, and 24 with values of 1.60 ng/mL (IQR, 0.61–3.35), 1.34 ng/mL (IQR, 0.72–2.68), and 2.24 ng/mL (IQR, 0.96–3.25), respectively. There was no significant difference among the positive rates of ADA at each interval.

The number of patients with and without ADA at each interval is shown in Fig. 3a. Treatment from week 4 to 24, three patients (5.00%) were continuously ADA positive; 28 patients (46.67%) were continuously ADA negative; 19 patients who were ADA-positive (31.67%) reverted to ADA-negative status, and 10 ADA-negative (16.67%) reverted to ADA-positive status.

Table 3 Correlations between the YSP level and improvement in clinical data at each interval compared to baseline

	Week 4		Week 12		Week 24	
	r	*p*	*r*	*p*	*r*	*p*
△BASDAI	0.120	0.366	0.417	0.001	0.346	0.008
△BASFI	− 0.218	0.103	0.022	0.875	0.048	0.720
△BASMI	− 0.055	0.681	− 0.063	0.643	− 0.027	0.839
△ASDAS-CRP	0.131	0.323	0.196	0.147	0.321	0.014
△ESR (mm/h)	0.034	0.797	0.041	0.766	0.163	0.222
△CRP (mg/L)	0.139	0.293	0.107	0.433	0.270	0.004
△TNF-α (pg/mL)	0.066	0.621	0.055	0.688	0.203	0.127

YSP, yisaipu; *BASDAI*, Bath Ankylosing Spondylitis Disease Activity Index; *BASFI*, Bath Ankylosing Spondylitis Functional Index; *BASMI*, Bath Ankylosing Spondylitis Measurement Index; *ASDAS-CRP*, Ankylosing Spondylitis Disease Activity Score-C-reactive protein; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *TNF*, tumour necrosis factor

Effect of ADAs on the YSP levels and clinical efficacy

We divided the patients into two groups at each interval based on whether they were ADA-positive. We found that the YSP levels were significantly higher in patients who were ADA-negative than those who were ADA-positive (2.46 ± 0.63 vs 1.97 ± 0.98 μg/mL, $p = 0.044$; 2.55 ± 0.94 vs 2.10 ± 0.58 μg/mL, $p = 0.023$ and 2.85 ± 1.09 vs 2.22 ± 0.74 μg/mL, $p = 0.042$ at weeks 4, 12, and 24, respectively). Furthermore, TNF-α levels were significantly lower in patients who were

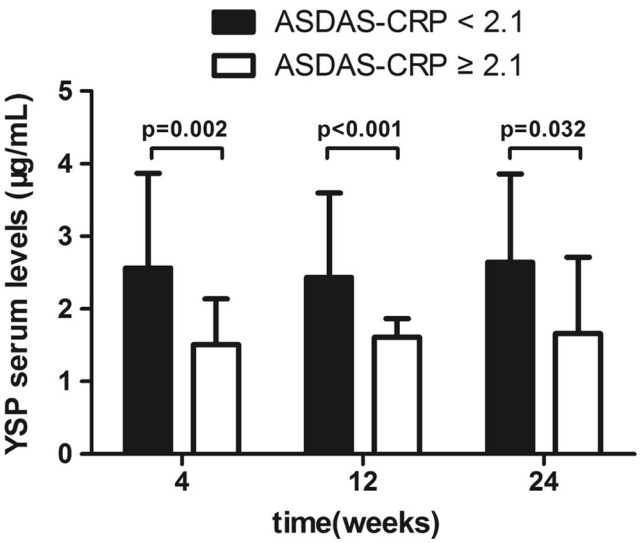

Fig. 1 YSP serum levels of patients with ASDAS-CRP < 2.1 and patients with ASDAS-CRP ≥ 2.1 at 4, 12, and 24 weeks. YSP, yisaipu; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score-C-reactive protein

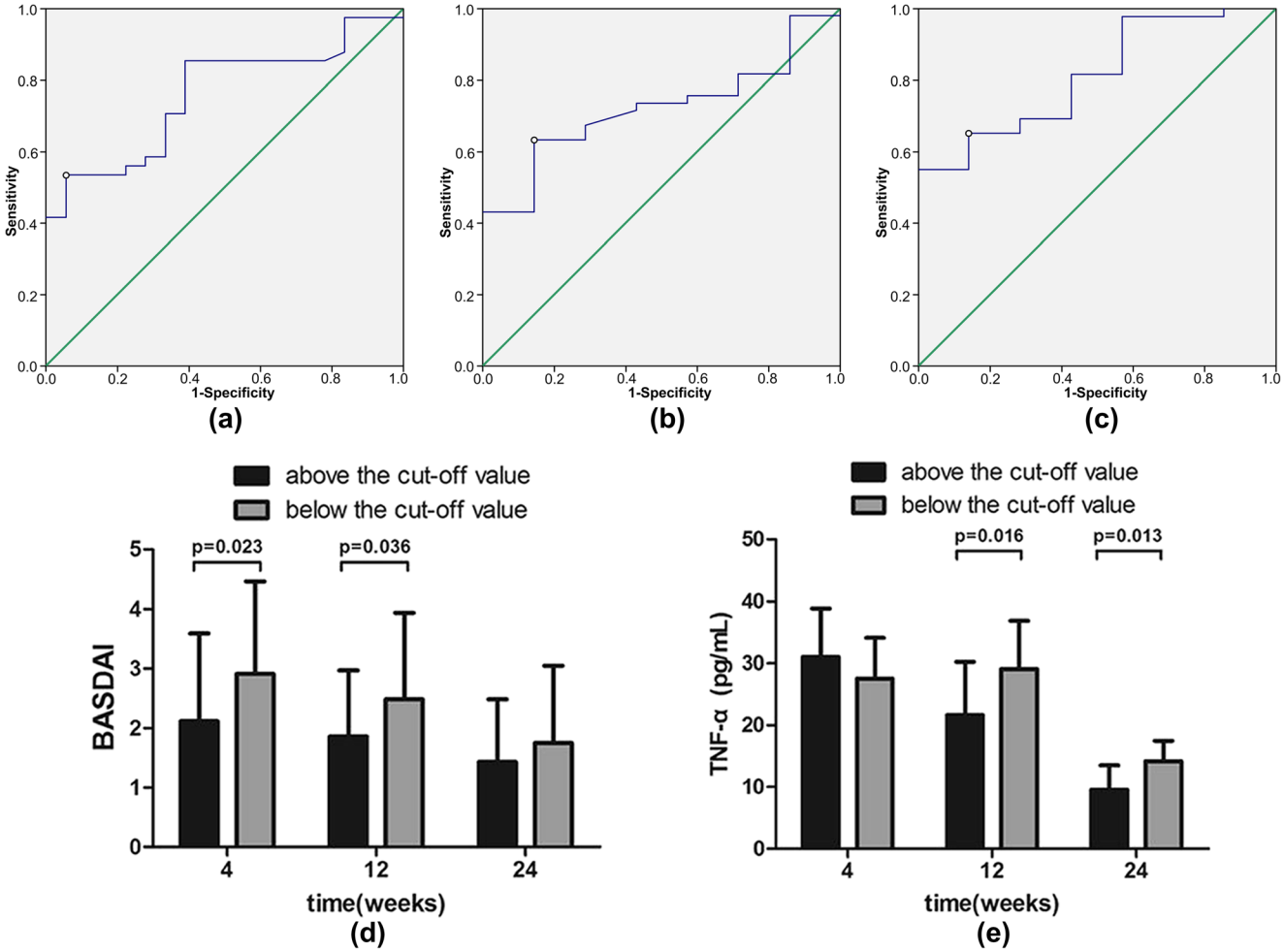

Fig. 2 Receiver-operating curves to determine the cut-off values of the YSP level at weeks 4 (a), 12 (b), and 24 (c). BASDAI (d) and TNF-α levels (e) of patients divided into two groups according to whether they achieved cut-off value of the YSP level at weeks 4, 12, and 24. YSP, yisaipu; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; TNF, tumour necrosis factor

ADA-negative than in those who were ADA-positive (28.24 ± 5.73 vs 33.71 ± 4.55 pg/mL, $p = 0.034$; 21.67 ± 9.19 vs 31.71 ± 5.75 pg/mL, $p = 0.008$ and 11.85 ± 3.97 vs 17.42 ± 6.29 pg/mL, $p = 0.036$ at weeks 4, 12, and 24, respectively, Fig. 3b, c).

In addition, we calculated the ASAS remission rates (proportion of the patients who reached at least ASAS 20) in the two groups at each interval. We found no significant difference between the ASAS remission rates of patients who were ADA-positive and ADA-negative (83.3% vs 85.7%, 84.2% vs 94.6%, and 100% vs 97.7% at weeks 4, 12, and 24, respectively).

Discussion

The efficacy of TNF-α inhibitors and their biosimilars in the treatment of AS has been widely accepted; however, some patients still show poor responses. Previous studies showed that the drug levels and ADAs of TNF-α inhibitors impacted the clinical efficacy [12–14], and therefore, it is necessary to monitor drug level and ADA of patients who received TNF-α inhibitor therapy. Our study not only showed that drug levels of etanercept biosimilar are associated with disease activity, but for the first time, also proposed effective serum level of etanercept biosimilar in Chinese patients with AS who achieved moderate or inactive disease activity (ASDAS-CRP < 2.1) at different period of therapy. Furthermore, we also discussed the effect of ADA on drug levels and clinical efficacy.

We found the YSP level increased rapidly within 4 weeks, the study by Kneepkens [9] supports our result on etanercept level, which might be attributable to the dose of 50 mg weekly administered. In our study, patients with the YSP levels above the cut-off value had lower BASDAI and lower TNF-α levels than in those who had levels below the cut-off value. If the YSP level of patients could reach the cut-off value as soon as possible, their disease activity might be controlled effectively. This could be considered as a reasonable guidance for the YSP therapy of Chinese patients with AS. At week 4 of treatment, patients with the YSP levels below the cut-off value had

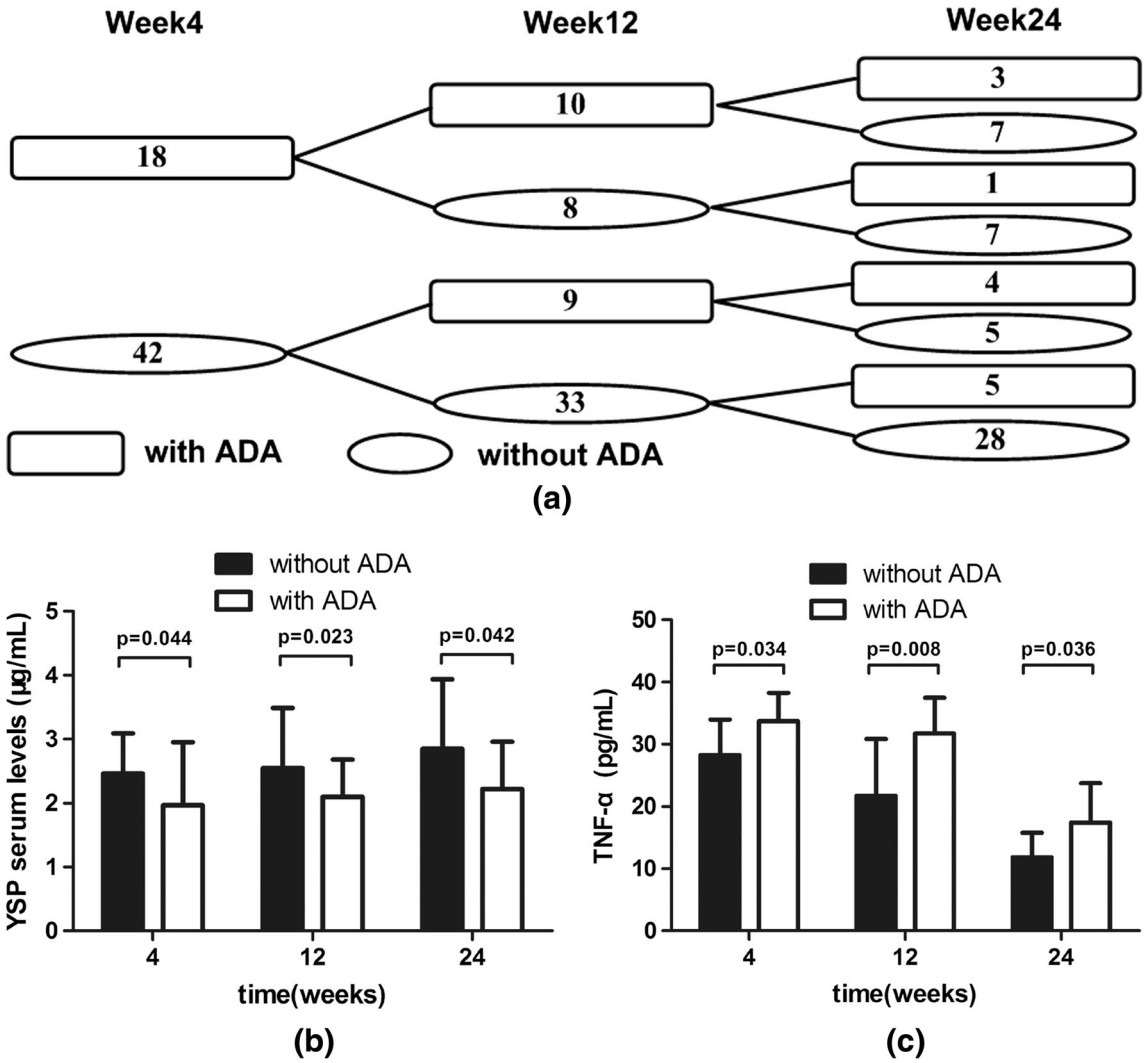

Fig. 3 Numbers of patients with and without ADA at weeks 4, 12, and 24 (a). YSP serum levels (b) and TNF-α levels (c) of patients divided into two groups according to whether they were ADA-positive at weeks 4, 12, and 24. ADA, antidrug antibodies; YSP, yisaipu; TNF, tumour necrosis factor

higher BMI. The study by Jamnitski [10] also found that a higher etanercept dosage needs to be assessed in patients with high disease activity and high BMI. Therefore, the BMI of patients may provide a basis for individualised therapy.

Patients who were ADA-positive exhibited lower YSP levels than those who were ADA-negative did, which indicated that the presence of ADA affected the YSP levels. The immune complexes of the YSP and ADA could cause rapid drug elimination and might result in lower YSP levels [23, 24]. de Vries et al. [12, 13] found that ADAs of infliximab and adalimumab were also associated with low drug levels. The positive rate of the anti-YSP antibody (21.67%) at the end of our study was similar to that of an anti-etanercept antibody (0%–18%) reported in recent studies, and we also found that the anti-YSP antibodies had no effect on ASAS remission rates. Nineteen patients who were ADA-positive (31.67% of the 60 patients, with an average duration of 3.95 weeks) converted to a negative status and 13 (21.67% of the 60 patients, with an average duration of 9.38 weeks) remained positive at the end of our study. Studies of monoclonal antibodies indicated that ADA could still be detectable after 54 weeks of infliximab treatment and 12 months of adalimumab treatment [13, 14]. Although the duration of ADA requires further elucidation, the short existence of ADA might be a possible explanation for their lack of clinical efficacy. However, de Vries et al. [12, 13] found that ADAs against monoclonal antibody were associated with poor clinical efficacy. Unlike monoclonal antibodies, the YSP investigated in our study, as a biosimilar of etanercept, is fusion protein TNF-α inhibitor.

In our study TNF-α level tended to decrease over time. Studies of etanercept found that anti-etanercept antibodies could bind to the fusion region of etanercept, but they left the TNF-binding site free, and therefore, the function of etanercept remained uncompromised [24]. As a biosimilar of etanercept, the YSP has similar structure and biological activity, which might be another reasonable explanation for the lack of efficacy of the anti-YSP antibodies on clinical efficacy. It has also been

reported that treating patients with rheumatoid arthritis and AS with etanercept could increase their TNF-α levels at the initial stage [25, 26]. This might be attributable to the different detection methods used. ELISA kits used in other studies detected free TNF-α and TNF-α-etanercept complexes [24], whereas in our study, we detected free TNF-α only.

Similar to all biologics, the YSP might cause a variety of adverse reactions [27, 28] and considerable financial burden [29]. Therefore, when patients show poor response to the YSP therapy, the detection of their YSP or ADA levels might be helpful for clinical guidance. It might be beneficial to adjust the dosage in patients with low YSP levels. Furthermore, for patients who develop a high ADA level, this may be addressed by adjusting the treatment strategy such as administering DMARDs or switching to other biologics.

According to the International ASAS consensus statement for the use of the anti-TNF agents in patients with AS [19], patients are administered a recommended dose and course of treatment. When patients with AS show good responses to the YSP treatments, and their YSP levels are maintained at an effective level, the course of treatment could be lengthened appropriately. Additionally, evidence suggests that the extended use of etanercept in patients with AS with low disease activity is feasible [30, 31]. Furthermore, a study has shown that low-dose etanercept treatment after patients achieve clinical remission could be an alternative treatment option for AS, but more than 24 weeks of standard-dose treatment before dose reduction may be beneficial for longer drug efficacy in this strategy [32].

There were some limitations to this study, such as the number of patients enrolled was limited, and our study period was only 6 months. In the future, we intend to increase the number of patients and extend the monitoring duration to discover the significance of YSP and ADA levels in clinical practice.

In conclusion, detecting drug and ADA levels might facilitate the estimation of treatment efficacy and adjustment of medication regimens during etanercept biosimilar therapy to achieve precision medicine in patients with AS.

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Contributors Yidian Dong contributed to the acquisition, analysis or interpretation of data, and drafting the manuscript. Ping Li contributed to the study conception and design. Tingshuang Xu contributed to the preservation of serum and supervision of the study. Liqi Bi contributed to the study conception and design and final approval of the version published.

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Compliance with ethical standards

Disclosures None.

Ethical statement This study was conducted in accordance with the ethical standards of the Helsinki Declaration and approved by the Ethical Committee of the China-Japan Union Hospital of Jilin University (approval number, 2015-wjw008). Each patient was selected following a rigorous process and provided written informed consent.

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