The efficacy of tocilizumab for the treatment of Chinese Takayasu's arteritis

J. Zhou[1], Z. Chen[1], J. Li[1], Y. Yang[1], J. Zhao[1], H. Chen[2], M. Liu[3], F. Sun[1], M. Li[1], X. Tian[1], X. Zeng[1]

[1]Department of Rheumatology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing, China;
[2]Department of Rheumatology, The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, China;
[3]Department of Rheumatology and Nephrology, Minzu Hospital of Guangxi Zhuang Autonomous region, Nanning, Guangxi, China.

*Jiaxin Zhou, MD**
*Zhe Chen, MD**
Jing Li, MD
Yunjiao Yang, MD
Jiuliang Zhao, MD
Hu Chen, MD
Min Liu, MD
Fei Sun, MD
Mengtao Li, MD
Xinping Tian, MD
Xiaofeng Zeng, MD

**These authors contributed equally to this study.*

Please address correspondence to:
Dr Xinping Tian and Dr Xiaofeng Zeng, Department of Rheumatology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 1 Shuaifuyuan Wangfujing Dongcheng District, Beijing, 100730 China.
E-mail: tianxp6@126.com, xiaofeng_zeng@cstar.org.com

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ABSTRACT

Objective. *The aim of this study was to evaluate the efficacy and safety of tocilizumab (TCZ) in Chinese Takayasu's arteritis (TAK) patients.*

Methods. *This was a single-centre prospective study. Sixteen consecutive TAK patients were included. Patients were treated with tocilizumab infusions with a dosage of 8 mg/kg. Serum inflammation markers including erythrocyte sedimentation rate (ESR) and hypersensitivity C-reactive protein (hsCRP) were recorded at baseline and before each TCZ infusion. Doppler ultrasonography was used to track vascular changes every 6 months during the study. The efficacy and safety profile of patients during the study were collected and analysed.*

Results. *Sixteen patients with a median age of 26.5 (18–47) were recruited and analysed. One patient was treatment naïve; the others had taken a median of 3 (1–5) conventional immune suppressants before TCZ therapy. Three patients withdrew TCZ after 1 infusion due to unbearable neck pain. The other 13 patients were treated with TCZ for a median of 13 (7–20) months. After TCZ treatment, the median ESR, hsCRP level, mural thickness of common carotid artery and subclavical artery decreased from 39 (7–92) mm/h, 28.88 (7.6–155.93) mg/L, 0.24 (0.06-0.59) cm, 0.18 (0.07–0.47) cm to 6 (1–30) mm/h ($p<0.001$), 0.59 (0.08–19.12) mg/L ($p=0.006$), 0.17 (0.04–0.53) cm ($p<0.001$), and 0.12 (0.07–0.18) cm ($p=0.035$) respectively. The glucocorticosteroid dosage was tapered or maintained in all patients. One episode of urinary infection was recorded and relieved after antibiotic therapy. Neither neutropenia nor abnormal liver enzyme was observed.*

Conclusion. *Our study suggests that TCZ is a safe and effective agent for long-term treatment in Chinese TAK patients.*

Introduction

Takayasu's arteritis (TAK) is a chronic systemic vasculitis which mainly affects the aorta and its major branches (1). Although TAK has been reported worldwide, Asians are the most susceptible population (2); it is a female predominant disorder (82.9–97.0%) and the median onset age is 25 (3).

Treatment of TAK remains a big challenge. Glucocorticoid (GC) is still the mainstay of treatment. Flare is a common experience among the majority of TAK patients when GC dosage tapers or is discontinued (4). Moreover, GC is not recommended for long-term use due to its adverse events (5). Traditional immunosuppressive agents such as cyclophosphomide, methotrexate and azathioprine have been used for TAK treatment though there is very limited evidence to support their efficacy in disease remission induction and maintenance therapy (6). Moreover, up to 30% patients could not achieve remission with traditional immunosuppressive agents (7). Recently, biologics that target tumour necrosis factor α (TNF-α) have been reported to be effective in some TAK patients (8). However, only 37% of TAK patients could reach complete remission and 20% of them experienced adverse events, including infection, allergic reaction, and malignancy (9). Tocilizumab (TCZ), a humanised anti-IL-6R antibody, was reported to be effective in treating patients with refractory TAK in several case reports, even in TNF-α inhibitors non-responders (10-15). These reports suggested that TCZ might be a promising agent for TAK treatment.

The aim of this study was to evaluate the long-term efficacy and safety of TCZ for TAK treatment. According to our knowledge, this is the first report on TCZ therapy in Chinese TAK patients and is also the largest prospective TA case series treated with TCZ so far.

Patients and methods

This was a prospective, single-centre study conducted by the Department of Rheumatology of Peking Union Medical College Hospital (PUMCH), a Chinese nationwide referral centre, from October 2014 to April 2016. This study was approved by the Institution Review Board (IRB) of PUMCH (no. S-478) and written informed consent was obtained from each patient. The study was registered in the Chinese Clinical Trial Registry system and the Trial Registration Number (TRN) was ChiCTR-OPC-16009231. The data of all the patients in the present study was recorded in the Chinese Rheumatism Data Center (CRDC) database (16).

Males and non-pregnant female patients aged older than 18 years, patients who fulfilled the TAK classification criteria of the American College of Rheumatology (ACR) (1), and patients diagnosed with active disease according to the National Institute of Health (NIH) criteria (3), whether they were treatment naïve or not, and those who had never received TCZ before were included into the study.

The exclusion criteria included:

1. Uncontrolled diabetes, hypertension before entry;
2. Active digestive tract bleeding within 3 months before entry;
3. History of primary or secondary immunodeficiency and malignant diseases;
4. Active infections that requires treatment, including bacteria, virus, fungi and mycobacteria infection;
5). Neutrophil counts $<1.0\times10^9$/L and/or platelet counts $<100\times10^9$/L;
6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >2 times the upper normal limit (UNL), and the serum creatinine level >1.5 UNL.

The demographic data, clinical manifestations, and medication history were collected before TCZ treatment. GC dosage (prednisone or equivalent) was recorded before and after TCZ treatment. Laboratory tests were measured before each TCZ infusion, including white blood cell (WBC) counts, haemoglobin (Hb), ALT, AST, serum creatinine, blood urea nitrogen, erythrocyte sedimentation rate (ESR) and hypersensitive C-reactive protein (hsCRP). The UNL of ALT, AST, ESR, and hsCRP were 40 U/L, 40 U/L, 20 mm/the first hour and 3 mg/L, respectively.

The blood vessel involvement patterns of TA were sub-classified according to Numano classification criteria as I, IIa, IIb, III, IV and V based on catheter angiogram or computer tomography angiogram (CTA) findings before entry (17). In this study, mural thickness at the thickest part of the vessel as well as the narrowest diameter of the lumen of common carotid artery (CCA) and subclavial artery (SCA) were measured by Doppler ultrasonography at the baseline and were repeated every 6 month during the followed-ups. The ultrasonographists were blinded to the treatment.

The first dosage of TCZ was 4 mg/kg intravenous infusion in those patients who had a history of allergy to any food or drug to decrease the chance of allergic reactions. The dosage of TCZ was increased to 8 mg/kg since the second infusion. For those patients who had no history of allergy, the initial dosage of TCZ was 8 mg/kg. After at least 6 monthly TCZ infusions, if the disease remained inactive according to the NIH criteria (3), the infusion interval was gradually extended to 12 weeks. TCZ was regarded as inefficacy and subsequently discontinued if (1) there was no decrease in both ESR and hsCRP levels measured at two consecutive TCZ infusions, or (2) the mural thickness of CCA or SCA increased or vascular stenosis deteriorated at two consecutive measurements by Doppler ultrasonography.

Adverse events were recorded at each visit. Neutropenia was defined as the neutrophil count less than 2×10^9/L. Abnormal liver enzymes were defined as the ALT or AST >2 times of UNL.

Statistic analysis

Statistical analyses were conducted by SPSS software (v. 20.0; SPSS Inc., Chicago, IL, USA). Numerical data was expressed as median (range min-max) or mean±SD while categorical data was expressed as percentage or number. Numerical data was compared with the paired-sample's *t*-test or the independent-sample's *t*-test. Categorical data was compared with the Fisher's exact test or the Chi-square test. All probabilities were two-sided, and *p*-values <0.05 were considered to be statistically significant.

Results

Patients' characteristics at baseline

Sixteen patients were included in the study. Only one patient was male (Table I). The median age was 26.5 (range 18–47) years, and the interval between symptoms onset and TCZ treatment was 24.5 (range 2–129) months. The most common Numano subtype was type I (43.75%), followed by type V (25.00 %) and IIb (18.75 %). No type III was observed in this group of patients. Nine patients had constitutional symptoms. Limb intermittent claudication presented in 7 patients. The most commonly discovered physical findings were vascular bruits (100%), bilateral blood pressure differences over 10 mmHg (87.50 %) and radial pulse weakness (68.75 %). Only 1 patient was treatment naïve, the other 15 patients had experienced at least one relapse when the dosage of GCs was tapered or discontinued and they had ever been treated with a median of 3 (range 1–5) traditional immunosuppressive agents before TCZ therapy. Cyclophosphomide, taken by 12 patients, was the most commonly used immune suppressive agent in this group of patients. Nine patients had taken mycophenolate mofetile before entering into the study. Two patients had received biological TNF-α inhibitors before TCZ treatment.

Efficacy

The first dosage of TCZ was 4 mg/kg in 7 patients while 9 patients were treated with TCZ 8 mg/kg initially. All patients were treated with 8 mg/kg TCZ from the second infusion. Due to newly onset unbearable neck pain or neck pain deterioration, 3 patients received only 1 TCZ infusion and withdrawal. Five patients were treated with TCZ monthly. Except for the 3 patients who received only 1 TCZ infusion, the other 13 patients received a median of 10 (range 7–15) TCZ infusions in 13 (range 7–20) months (Table I). No pa-

Table I. Baseline demographics, disease characteristics, number of TCZ doses and duration of follow-up.

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Gender	F	F	F	F	F	F	F	F	M	F	F	F	F	F	F	F
Age (years)	31	47	25	19	25	22	31	28	31	27	26	18	28	28	24	25
Disease duration (months)	26	129	28	20	38	50	12	14	21	23	20	9	50	48	40	2
Numano subtype	IIb	IIb	V	I	I	I	V	V	I	V	IIa	I	IIb	I	IV	I
Constitutional symptoms[#]	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N
Limb claudication	N	Y	N	Y	Y	Y	N	Y	N	N	Y	Y	N	N	N	N
Neurological complaints[*]	N	Y	Y	N	N	N	N	N	Y	N	N	N	N	N	N	N
Vascular bruits	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
pulse weakness	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	Y
Bp[§] differences over 10 mmHg	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Carotidynia	N	N	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y
AR detected by UCG	N	N	Y	N	N	N	N	N	Y	Y	Y	N	Y	N	N	N
GC dosage (mg)	10	10	10	10	25	40	30	60	10	7.5	40	60	40	40	10	60
Number of TCZ infusions	12	15	13	9	10	12	10	15	13	7	1	1	1	10	8	9
Follow-up duration (months)	15	18	20	12	16	13	14	15	13	7	1	1	1	11	8	9

Y: yes; N: no. [#]Constitutional symptoms included fever, fatigue and emaciation. [*]Neurological complaints included dizziness, blurred vision, syncope, and stroke. [§]Bp: blood pressure; AR: aortic regurgitation; UCG: echocardiography; GC: glucocorticoid; TCZ: tocilizumab.

tient discontinued TCZ due to lack of efficacy during TCZ treatment.

Among the 13 patients who received at least 6 TCZ infusions, their ESR decreased from 39 (range 7–92) mm/h before TCZ treatment to 6 (range 1–30) mm/h (p<0.001) at the end of study, and hsCRP decreased from 28.88 (range 7.6–155.93) mg/l to 0.59 (range 0.08–19.12) mg/l (p=0.006), respectively (Fig. 1A-B). Elevated ESR or hsCRP levels were observed in 3 patients before the last TCZ infusion. The haemoglobulin level was increased from 119 (range 94–133) g/L at baseline to 129 (range 95–150) g/L before last TCZ infusion (p=0.024) (Fig. 1C). WBC decreased from 7.39 (range 4.54–13.84)×10^9/L to 5.99 (range 3.80–9.98)×10^9/L, which was not statistically significant (p=0.068).

After TCZ therapy, the mural thickness of CCA and SCA decreased from 0.24 (range 0.06–0.59) cm to 0.17 (range 0.04–0.53) cm (p<0.001), and from 0.18 (range 0.07–0.47) cm to 0.12 (range 0.07–0.18) cm (p=0.035), respectively (Fig. 1D-E). During the TCZ treatment, newly onset mural thickness occurred only in 1 subclavical artery without ESR or hsCRP elevation, however, which was gradually decreased with continuous TCZ infusion during the subsequent follow-up (Patient 6). The diameter of the lumen of CCA and SCA maintained stable or improved.

The mean GC dosage of the 13 patients before TCZ treatment was 24.80±19.54 mg (prednisone or equivalent), which was gradually tapered to 7.88±3.93 mg (prednisone or equivalent) at the last TCZ infusion (p=0.006) (Fig. 1F). One patient discontinued GC. Moreover, 7 patients could decrease their mean daily GC dosage by more than 50% while

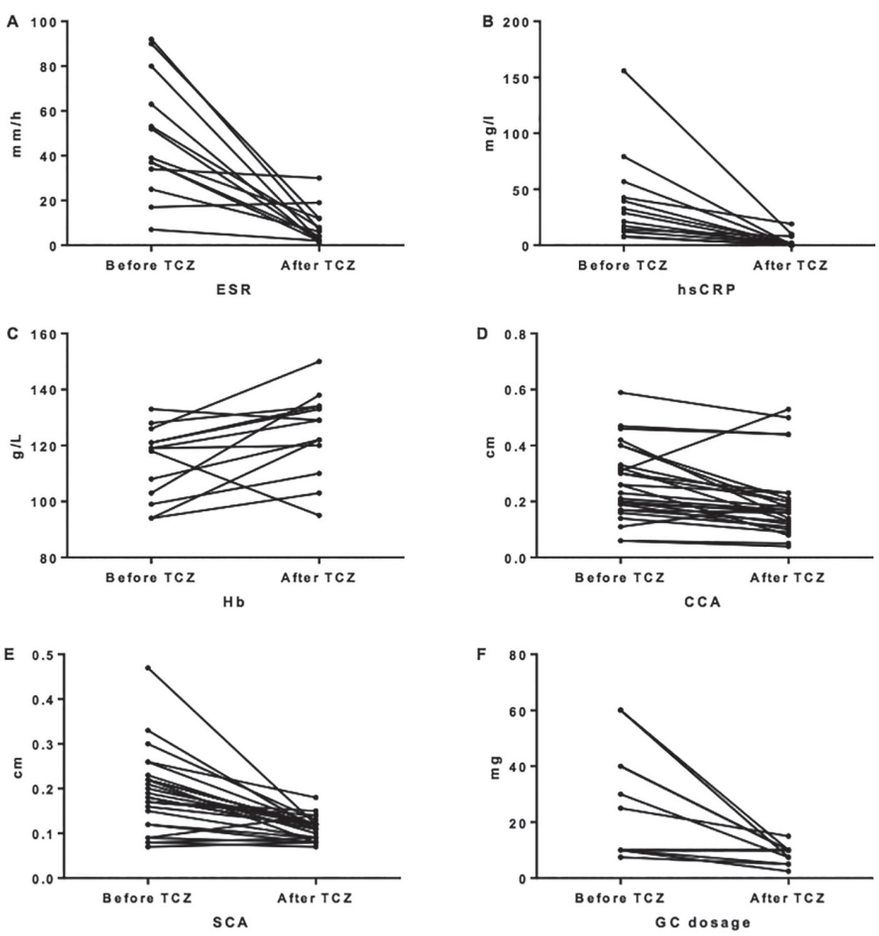

Fig. 1. Laboratory tests, vessel mural thickness and GC dosages before and after TCZ infusions. ESR: erythrocyte sedimentation rate; hsCRP: hyper-sensitive C-reactive protein; Hb: haemoglobin; CCA: common carotid artery; SCA: subclavical artery;. GC: glucocorticoid.

their disease remained stable. Three patients maintained their daily GC dosage at 10 mg during the whole study period.

Safety profile

In this study, neither neutropenia nor liver enzyme abnormality was observed. One patient was diagnosed as urinary infection during TCZ treatment and recovered after antibiotic treatment.

Six patients complained of newly onset or deteriorated neck pain after the first or second TCZ infusion. The neck pain was unbearable even after pain control therapy in 3 (50%) patients. This led to discontinuation of TCZ treatment, while neck pain disappeared with continuous TCZ infusions in another 3 patients. Among these 6 patients, 2 patients were Numano subtype I, 2 were subtype V, and the other 2 were subtype IIa and IIb, respectively. Age and disease duration between patients with and without neck pains were not statistically different (25.50±4.72 *vs*. 28.20±7.48 years, p=0.443; 25.83±19.06 *vs*. 37.50±34.58 months, p=0.463). Patients with neck pain were more likely to suffer from constitutional symptoms (100% *vs*. 30%, p=0.011). Patients with neck pain had higher GC dosage (prednisone or equivalent) and lower Hb concentration compared to those without (48.33±13.29 *vs*. 19.25±17.56 mg, p=0.004; 101.83±9.78 *vs*. 118.70±9.38 g/L, p=0.004). The WBC, ESR and hsCRP levels among patients with neck pain were higher than those without. However, no statistically significant difference was detected (10.00±3.08 *vs*. 8.09±2.96 $\times 10^9$/L, p=0.241; 66.00±29.63 *vs*. 49.90±29.46 mm/h, p=0.309; 80.26±55.66 *vs*. 40.52±46.78 mg/L, p=0.147). The mural thickness of CCA and SCA between patients with and without neck pain was not statistically different (0.25±0.08 *vs*. 0.26±0.14, p=0.847; 0.19±0.08 *vs*. 0.20±0.09, p=0.732).

Discussion

TAK is a rare systemic vasculitis which occurs predominantly among the eastern Asian population. Due to the rarity of the disease and difficulty in disease activity assessment, no randomised clinical trial was conducted for the treatment of TAK. The treatments used in clinical practice were mostly empirical or anecdotal. TAK treatment remained a challenge.

IL-6 is a powerful pleiotropic cytokine which is crucial for the differentiation of T/B lymphocytes and Th 17 cells infiltrated in the artery walls of TA (7, 18). In addition, IL-6 may induce hepatocytes synthesising acute phase proteins, such as C-reactive protein (CRP), a commonly used marker for active TAK (7). It is proposed that IL-6 per se may be a sensitive biomarker for monitoring disease activity since it is elevated in both serum and aortic tissues of untreated patients (18). Emerging data has shown that TCZ may be effective for TAK. Goel *et al*. (13) reported that TCZ could control TAK activity rapidly. In their study, 6 out of 10 patients maintained stable in clinical and radiological presentations, as well as acute phase reactants after 6 infusions of TCZ. The GC dosage was also decreased. However, disease flare occurred in 50% of patients after TCZ discontinuation. In a multicentre, retrospective study carried out by Mekinian *et al*. (11), all 7 patients responded completely at the 6th month of TCZ treatment and remained stable at the 12th month with monthly TCZ infusion. Nakaoka *et al*. treated 4 patients with monthly TCZ and found that the acute phase proteins such as CRP and serum amyloid A (SAA) were decreased to normal levels within one month and maintained stable thereafter. Two of the four patients also had improvement of mural thickness after TCZ treatment. Moreover, GC dosages were tapered in all the patients without clinical flares during the TCZ therapy (12). Salvarani *et al*. reported 2 patients with TAK whose standardised uptake values (SUV) at PET/CT were remarkably decreased after 6 doses of TCZ infusions monthly together with remarkable reduction in ESR/CRP, GC dosages and ITAS scores (14).

Although some of our patients received TCZ treatment with extended interval due to the high cost, favourable responses were obtained which were similar to the published studies. Among the 13 patients who received TCZ therapy for more than 6 infusions, no patient withdrew TCZ due to lack of effectiveness. Remarkable decrease in acute phase reactants and reduction of GC dosage were observed after TCZ treatment.

Anaemia is quite common among patients with chronic autoimmune disease including TAK (20). IL-6, TNF-α, and IL-1 have been demonstrated to contribute to the occurrence of anaemia (20). In our study, the mean Hb concentration was increased by 16 g/L after TCZ treatment, reflecting improvement in anaemia after the disease was controlled. TCZ would be effective in patients who were refractory to biological TNF-α inhibitors (21). Two of our patients achieved stable disease during TCZ treatment after failing to respond to biological TNF-α inhibitors.

Recently, more and more data have shown that Doppler ultrasonography is a cost-efficient and reliable modality for early diagnosing of TAK (22). Circumferential and homogeneous mural thickness is the distinctive and early findings of TAK by ultrosonography (23), and the findings may be correlated with disease activity (23, 24). Thus, Doppler ultrasonography may be one of the image modalities that could be used to monitor disease activity and response to treatment in TAK patients (22). In our study, the mural thickness of both CCA and SCA were remarkably decreased after TCZ treatment. Moreover, during TCZ infusions, only one newly onset mural thicken was observed, which was gradually decreased with continued TCZ infusion during follow up. No new stenosis occurred during follow-ups.

TCZ is safe in long term treatment for rheumatoid arthritis and systemic juvenile idiopathic arthritis (25, 26). The most common adverse effects were infection and liver damage, however, the majority was mild. Transient decreases in neutrophil counts were sometimes observed, however, neutropenia was rare (25, 26). In our study, only one episode of infection was observed which was relieved after antibiotic therapy.

No neutropenia and abnormal liver enzyme was observed.

It was interesting that 6 patients complained of newly-onset or deteriorated neck pains after TCZ infusions, which had never been reported in the literature before. Further analysis showed that patients with constitutional symptoms, higher GC dosages and lower Hb concentrations at enrolment were more likely to suffer from this complication. Furthermore, in our study, all neck pain deteriorations were observed after the first or second TCZ infusions when TAK disease activity was high. Moreover, the inflammatory markers (ESR/hsCRP/WBC) were higher among those with neck pain after TCZ infusions, though the differences were not statistically significant. All the aforementioned results indicated that high acute or chronic systemic inflammation correlated with neck pains after TCZ infusions. However, the precise aetiology remains unknown.

There are several limitations in our study. First, although our study was the largest patient series so far in the literature about TAK treated with TCZ, the number of patients enrolled was still small. Second, only CCA and SCA mural thickness were assessed, the lesions of other involved arteries were not included for analysis. Therefore, further studies are needed to confirm the results of this study.

Conclusion

The results of our study suggest that TCZ is a safe and effective biologic agent for long-term use in patients with TAK, especially in those with refractory courses. However, large and randomised clinical trial is needed in future studies.

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