Circulation levels of acute phase proteins in patients with Takayasu arteritis

Jun Ma, MD, Xiaoyun Luo, MD, Qinghua Wu, MD, Zhong Chen, MD, Lei Kou, MD, and **Haitao Wang, MD,** *Beijing, China*

Objective: **Takayasu arteritis (TA) is an immune-mediated disease with an unknown etiology. Assessment of disease activity in patients with TA is challenging owing to the absence of reliable serologic markers. Because circulation levels of acute-phase proteins fluctuate with the severity and extent of the inflammatory reaction, they may be potential biomarkers for the identification of TA activity. To test this hypothesis, certain acute-phase proteins were examined in TA patients and controls.**

Methods: **The study included 43 prospectively selected TA patients, with 18 in active phase and 25 in inactive phase. The Sharma modified criteria were used for disease diagnosis, and the National Institutes of Health criteria were used for TA activity assessment. Circulation levels of acute-phase proteins, including serum amyloid A (SAA), fibrinogen, complement C4-binding protein (C4BP), C-reactive protein, serum amyloid P, haptoglobin, α-acid glycoprotein, transthyretin, α1-microglobin, and complement fraction C3c and C4a were investigated by enzyme-linked immunosorbent assay in each participant.**

Results: **Circulating levels of SAA and C4BP were significantly increased in active TA patients compared with inactive TA patients and in controls, with (SAA: 95.9 [interquartile range, 51.9] vs 49.2 [82.0], $P = .009$; and 23.9 [50.1] mg/L, $P = .001$, respectively; C4BP: 88.5 [72.6] vs 61.7 [57.7], $P = .023$; and 32.6 [32.1] mg/L, $P < .001$, respectively). The levels of both proteins in inactive TA patients were still higher than those in controls (SAA: 49.2 [82.0] vs 23.9 [50.1] mg/L, $P = .021$; C4BP: 61.7 [57.7] vs 32.6 [32.1] mg/L, $P = .025$). No difference was found in the levels of the other acute-phase proteins studied.**

Conclusions: **SAA and C4BP may be useful biomarkers in determining the disease activity of TA. More work should be done to test these results in a large cohort of patients in a longitudinal manner. (J Vasc Surg 2010;51:700-6.)**

Clinical Relevance: **Disease activity assessment in patients with Takayasu arteritis is important but difficult because of the absence of reliable serologic markers. The concentration of acute-phase proteins, a group of liver-derived plasma proteins, changes greatly in inflammatory disease. This study investigated the circulation levels of acute-phase proteins in Takayasu arteritis patients with different disease activity and in healthy controls and evaluated their possibility as biomarkers for activity judgment in this disease.**

Takayasu arteritis (TA) is a rare, chronic inflammatory vasculitis that mainly affects the large elastic arteries, such as the aortic arch and its primary branches, leading to stenosis, occlusion, or aneurysm formation in vessels.[1] Infectious agents, autoimmunity, and genetic factors are considered to play a major role in the physiopathology of this disease.[2]

In the natural course of TA, the patient experiences cycles of active and inactive phases that reflect the different inflammatory states of the arterial lesions. Treatment strategies of the two phases are quite different. In the active phase, immunosuppressive and cytotoxic agents are usually used to control the development of inflammation, relieve the symptoms, and restrict the extent of affected arteries. The aim during the inactive phase, however, is to closely monitor disease activity. Any necessary vascular reconstructive operations or endovascular interventions are performed preferably in this phase.[3,4] Clinicians must carefully assess and identify the phase of disease activity before a proper treatment plan is made; however, a reliable, convenient, and efficient serologic marker is still unavailable.

An acute-phase protein is defined as one whose plasma concentration increases (positive acute-phase protein) or decreases (negative acute-phase protein) by at least 25% during inflammatory disorders.[5] Commonly, serum levels of acute-phase proteins begin to elevate within a few hours after the initial stimulation and return to a normal level in a few days. If the etiologic factors persist, however, this process can be prolonged and become a chronic reaction.

In our previous work, we explored the spectrum of plasma proteins in TA patients by means of proteomics (data not published). Serum amyloid A (SAA), fibrinogen, complement C4-binding protein (C4BP), C-reactive protein (CRP), serum amyloid P (SAP), haptoglobin, α-acid glycoprotein (AAG), transthyretin, α1-microglobin (AMG), and complement fraction C3c and C4a were expressed more frequently compared with healthy controls. All these

From Vascular Surgery Department, Anzhen Hospital affiliated to Capital Medical University.

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Reprint requests: Qinghua Wu, MD, Vascular Surgery Department, Anzhen Hospital affiliated to Capital Medical University, Anzhen Li, Chaoyang District, Beijing, China, 10029 (e-mail: ma_dayong@yahoo.cn).

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proteins belong to the family of acute-phase proteins. Because TA is characterized by alterations of acute and chronic inflammatory reactions in the three layers of the arterial wall, circulating levels of acute-phase proteins may change with this pathologic course.

The objectives of this study were to determine whether the levels of acute-phase proteins were altered in TA patients in the different activity phases compared with healthy controls. To the best of our knowledge, this is the first time that a group of acute-phase proteins have been quantitated and characterized in TA patients.

MATERIALS AND METHODS

The study protocol was in agreement with the guidelines of the Declaration of Helsinki and was approved by the Ethics Board of the Capital Medical University, Beijing, China. All participants provided informed consent.

Patients and controls. The study included 43 prospectively selected patients with TA who had been referred to the Vascular Surgery Department of Anzhen Hospital affiliated with the Capital Medical University of China from September 2006 to October 2008. The diagnosis of TA was based on clinical symptoms, physical examination, laboratory findings, and angiographic results. The patients fulfilled the Sharma modified criteria for the clinical diagnosis of TA by a sensitivity of 92.5% and a specificity of 95%.[6]

Patients were excluded from the study if they had one of the following four conditions: (1) a history of autoimmune disease, such as systemic lupus erythematosus or rheumatoid arthritis; (2) a history of trauma or surgical operation ≤1 month; (3) a history of cardiovascular or cerebrovascular event (eg, myocardial infarction or stroke), or (4) an acute or chronic inflammatory condition, such as acute bacterial or viral infection, or chronic inflammatory bowel disease, among others.

Disease activity was evaluated by the National Institutes of Health (NIH) criteria.[7] Briefly, patients who had new-onset or worsening of each of the following four features were scored 1:

1. the presence of systemic features such as fever or musculoskeletal problems (no other cause identified);
2. an elevated erythrocyte sedimentation rate (ESR);
3. the presence of features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruits, vascular pain (carotodynia), or asymmetrical blood pressure in upper or lower limbs; and
4. typical angiographic features.

Patients with a score of 0 or 1 were defined as inactive TA. Patients with a score of 2, 3, or 4 were defined as active TA.

The vascular lesions of each participant with symptoms suggestive of an active phase of TA were inspected by angiography or a computed tomography angiogram. In other participants, the absence of new vascular lesions was verified by ultrasound imaging, computed tomography angiography, or magnetic resonance angiography According to the criteria, 18 patients were in the active phase and 25 were in the inactive phase when they were registered in the study. Six patients were receiving medical immunosuppressive therapies by prednisone (1 mg/kg/d), two patients were receiving a maintenance dose of prednisone (5 to 10 mg/d), and one patient was taking cyclophosphamide (25 mg/d).

Angiographic features were classified according to the International TA Conference angiographic classification in Tokyo 1994 as follows:

- type I—involvement of the main branches from the aortic arch;
- type IIa—involvement of the ascending aorta, aortic arch, and its branches;
- type IIb—involvement of the ascending aorta, aortic arch and its branches, and thoracic descending aorta;
- type III—involvement of any or all of the thoracic descending aorta, abdominal aorta, or renal arteries;
- type IV—involvement of the abdominal aorta or renal arteries, or both; and
- type V—the combined features of types IIb and IV.[8]

The control group consisted of 20 age- and gender-matched healthy volunteers who were a mean age of 27.45 ± 5.80 years (range, 21-46 years). They had no clinical history of cardiovascular disease, collagen disease, or autoimmune disease, and no current inflammatory state. Their ethnic origins and socioeconomic backgrounds were similar to the TA participants.

Blood sampling. After an overnight fast, 10 mL of venous blood was collected in the morning from the medial cubital vein into a plain sterile tube for serum and into a heparinized tube for plasma. Serum and plasma were separated ≤1 hour and stored at −80°C until further analysis.

Biochemical laboratory investigations. A baseline biochemical investigation was initiated in all the participants, including a hemogram, urine analysis, and blood biochemistry test. The ESR was also measured using the Westergreen method.

Test of acute-phase proteins. A commercially available enzyme-linked immunosorbent assay (ELISA) kit was used to test SAA, fibrinogen, C4BP, SAP, haptoglobin, AAG, transthyretin, AMG, and complement fraction C3c and C4a according to the manufacturer's instructions (Uscnlife Sciences & Technology Co. Ltd Wuhan, China). CRP was measured by latex agglutination turbidimetric immunoassay (Uscnlife Sciences & Technology).

Statistical analysis. Data are expressed as mean ± standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Accordingly, analysis of variance and least significant difference tests, and Kruskal-Wallis and Wilcoxon rank sum tests were used to compare the differences between groups, when appropriate. The analysis was conducted with SPSS 13.0 software (SPSS Inc, Chicago, Ill), and values of $P < .05$ were considered to be statistically significant.

Table I. Clinical characteristics of the participants

Demographics	*Active TA (n = 18)*	*Inactive TA (n = 25)*	*Total TA (n = 43)*	*Controls (n = 20)*
Age, mean ± SD, y	25.17 ± 7.88	30.56 ± 12.04	28.30 ± 10.74	27.45 ± 5.80
Female/male	16:2	22:3	38:5	18:2
Vessel involvement, No. (%)				
Type I	7 (16.3)	9 (20.9)	16 (37.2)	. . .
Type IIa	1 (2.3)	2 (4.7)	3 (7.0)	. . .
Type IIb	0 (0]	2 (4.7)	2 (4.7)	. . .
Type III	2 (4.7)	1 (2.3)	3 (7.0)	. . .
Type IV	2 (4.7)	4 (9.3)	6 (14.0)	. . .
Type V	6 (14.0)	7 (16.3)	13 (30.2)	. . .
Medication				
Prednisone	6	2	8	. . .
Cyclophosphamide	0	1	1	. . .

SD, Standard deviation; *TA,* Takayasu arteritis.

Table II. Results of laboratory biochemical investigations

Investigations	*Active TA[a] (n = 18)*	*Inactive TA[a] (n = 25)*	*Total TA[a] (n = 43)*	*Controls[a] (n = 20)*
ESR, mm/h	39.1 ± 24.8[b,c]	15.2 ± 9.6	25.2 ± 21.0[b]	11.3 ± 5.1
Elevated ESR, No. (%)	15 (83.3)	7 (28)	22 (51.2)	0 (0)
Hemoglobin, g/dL	10.1 ± 1.7[b]	10.7 ± 1.4[b]	10.5 ± 1.6[a]	13.2 ± 1.2
White blood cells, 10^9/L	8.2 ± 2.3	8.3 ± 1.7	8.27 ± 1.99	7.5 ± 1.3
Platelets, 10^9/L	206 ± 53	185 ± 51	196 ± 52	201 ± 40
Fasting blood glucose, mmol/L	4.81 ± 0.92	4.62 ± 0.69	4.71 ± 0.79	5.02 ± 0.80
Urea, mmol/L	5.37 ± 1.52	6.04 ± 1.72	5.76 ± 1.66	5.43 ± 1.44
Creatinine, umol/L	69.6 ± 23.0	76.9 ± 24.9	73.9 ± 24.2	67.3 ± 21.4
Cholesterol				
Total, mmol/L	4.42 ± 1.06	4.34 ± 1.28	4.38 ± 1.18	4.92 ± 1.04
Triglyceride, mmol/L	1.14 ± 0.34	1.05 ± 0.38	1.08 ± 0.36	0.90 ± 0.42
LDL, mmol/L	2.10 ± 0.83	2.32 ± 0.99	2.23 ± 0.92	2.08 ± 0.65
HDL, mmol/L	1.71 ± 0.44	2.01 ± 1.07	1.88 ± 0.87	1.84 ± 0.54

ESR, Erythrocyte sedimentation rate; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *TA,* Takayasu arteritis.
[a]Unless otherwise indicated, data are expressed as mean ± standard deviation.
[b]$P < .05$ vs control group.
[c]$P < .05$ vs inactive TA group.

RESULTS

Clinical features of the participants. The clinical features of the study participants are summarized in Table I. A total of 43 TA patients with 18 in active phase and 25 in inactive phase, together with 20 healthy controls, were included and divided into three groups accordingly. Mean ages of the active-phase TA, inactive-phase TA, and the control groups were, respectively, 25.17 ± 7.88, 30.56 ± 12.04, and 27.45 ± 5.80 years. The female/male ratios of the TA groups and the control group were 7.6:1 and 9:1, respectively.

The angiographic classification data indicated that vessels above the aortic arch, including the subclavian, carotid, and the innominate arteries (type I) were the most commonly involved in the TA group (16 of 43), the next commonest pattern was type V (13 of 43). Nine patients (21%), six in active phase and three in inactive phase, were receiving immunosuppressive treatments when the study began.

Laboratory investigations. ESR was more frequently elevated in active-phase patients (83.3%) than in inactive-phase patients (28%; Table II). The mean ESR was 39.1 ± 24.8 mm/h in active TA compared with 15.2 ± 9.6 mm/h in inactive TA ($P < .001$) and 11.3 ± 5.1 mm/h in controls ($P < .001$). However, a lower hemoglobin level was detected in both TA groups compared with the control group (10.1 ± 1.7 in active and 10.7 ± 1.4 in inactive vs 13.2 ± 1.2 g/L in controls, both $P < .001$). No difference was noted between groups with respect to the other variables analyzed.

Levels of acute-phase proteins. This study analyzed 11 acute-phase proteins. The normality of data was tested by Kolmogorov-Smirnov test. The results of C3c, transthyretin, and AMG were normally distributed and are given as mean ± SD. The other results were non-normally distributed and are given as median (IQR).

Plasma levels of SAA were significantly raised in patients with active TA compared with patients with inactive TA and the controls (95.9 [51.9] vs 49.2 [82.0], $P = .009$ and 23.9 [50.1] mg/L, $P = .001$, respectively). At the same time, SAA levels of inactive TA patients were significantly higher than that of the controls (49.2 [82.0] vs 23.9 [50.1]

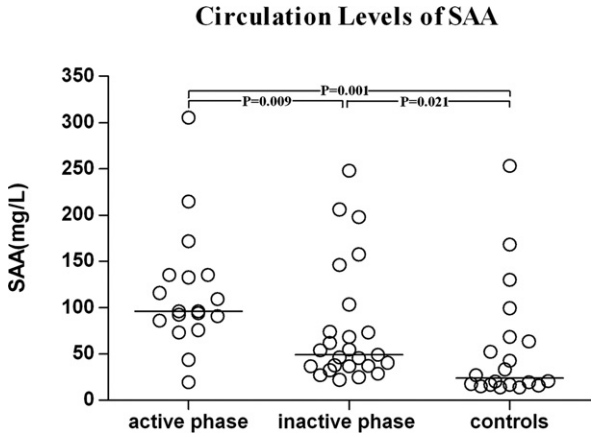

Fig 1. Scatter plot shows the circulation levels of serum amyloid A *(SAA)* in 18 active-phase Takayasu arteritis (TA) patients, 25 inactive-phase TA patients, and 20 healthy controls. The *bar* represents the median concentration of each group.

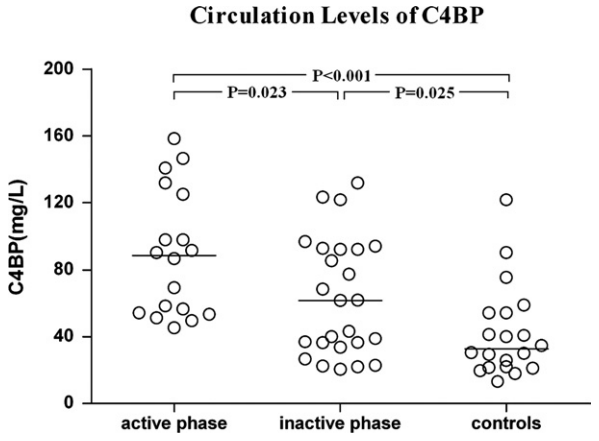

Fig 2. Scatter plot shows the circulation levels of complement C4-binding protein *(C4BP)* in 18 active-phase Takayasu arteritis (TA) patients, 25 inactive-phase TA patients, and 20 healthy controls. The *bar* represents the median concentration of each group.

mg/L, $P = .021$). SAA plasma levels for each participant are shown in Fig 1.

We also observed a significant elevation of C4BP levels in the plasma of active TA patients (88.5 [72.6] mg/L) compared with the inactive patients (61.7 [57.7] mg/L, $P = .023$) and the controls (32.6 [32.1] mg/L $P < .001$). When the plasma C4BP levels were compared between patients with inactive TA and the controls, a statistical difference was still detected ($P = .025$). The measured levels of C4BP in the study participants are shown in Fig 2.

Table III gives the results of all the acute-phase protein levels that were investigated. Except for SAA and C4BP, no statistical difference between the three groups was found in the levels of CRP ($P = .116$), fibrinogen ($P = .150$), haptoglobin ($P = .645$), AAG ($P = .110$), SAP ($P = .168$), transthyretin ($P = .112$), C3c ($P = .513$), C4a ($P = .784$), and AMG ($P = .193$).

DISCUSSION

The etiology and the underlying mechanism of TA are still far from clarified. Various studies have elucidated the importance of an immune-mediated mechanism in the development of TA.[9] In the active phase, TA is characterized as infiltration of lymphocytes and monocytes in the arterial wall, and at the same time, large amounts of cytokines and inflammatory factors are released to the circulation. As coming to the inactive phase, degradation of the elastic layer and fibrosis of the adventitia and media are the predominant alterations. Most patients with TA experience one or more cycles from the active phase to remission, then relapse.

The terms *active* and *inactive* are a reflection of different inflammatory states on the arterial wall. Accurate evaluation of disease activity in TA patients is important to avoid severe and various side effects from overuse of immunosuppressive drugs. It is also critical for surgeons to determine an appropriate operation time, because surgical interventions during the active phase usually cause a higher reintervention rate and more complications than those done in the inactive phase.[4,10] However, our ability to assess the disease activity in patients with TA is quite limited due to the absence of definitive tests for this purpose.[11]

Acute-phase proteins are a group of liver-derived plasma proteins induced and regulated by cytokines and inflammatory factors such as interleukin-6, interleukin-1, and growth factor.[12-15] The concentration of acute-phase proteins is correlated to the degree and extent of the inflammatory lesions. Normally, the level rises immediately after the initiation of the tissue inflammatory reaction, lasts for a few days, and then returns to normal levels. But the alteration can be prolonged and converted to a chronic response if the stimulus or low-grade inflammation continues.

In clinical practice, levels of acute-phase proteins are usually investigated to get valuable information on the presence and degree of inflammatory diseases.[16] Some acute-phase proteins have been considered among the strongest predictors of cardiovascular events in the general population and in patients with diabetes.[17,18] Because TA is a typical immune-mediated disease, it is possible that levels of acute-phase proteins fluctuate with the inflammatory state of the lesions on the vessels. They also may be useful in the observation of disease activity. To test this supposition, we investigated the concentration of a group of acute-phase proteins in patients with TA and healthy controls.

The clinical data from the 18 active-phase and 25 inactive-phase TA patients included in this study showed similarities with data from previous reports. First, TA affects young women more frequently. The mean age in our study was 28.30 years in the TA group, and the ratio of women to men was 7.6:1, which was similar to the reports of Korean (6:1) and Mexican (6.9:1) patients, but lower than that of

Table III. Circulation levels of active-phase proteins

Active-phase proteins	*Active TA group*		*Active TA group*		*Control group*		
	No.	*Median (IQR) or Mean ± SD*	*No.*	*Median (IQR) or Mean ± SD*	*No.*	*Median (IQR) or Mean ± SD*	P[a]
Serum amyloid A, mg/L	18	95.9 (51.9)	25	49.2 (82)	20	23.9 (50.1)	.001
C4BP, mg/L	18	88.5 (72.6)	25	61.7 (57.7)	20	32.6 (32.1)	.001
C-reactive protein, mg/L	18	6.65 (18.1)	25	2.3 (5.75)	20	2.28 (1.58)	.116
Fibrinogen, g/L	18	3.82 (2.26)	25	3.23 (3.95)	20	3.19 (2.77)	.15
Haptoglobin, g/L	18	1.73 (2.53)	25	1.81 (1.72)	20	1.32 (1.69)	.654
α-Acid glycoprotein, g/L	18	189.4 (310.3)	25	176.9 (102.6)	20	226.6 (304.4)	.11
Serum amyloid P, mg/L	18	43.3 (65.7)	25	49.3 (116.9)	20	36.9 (62.7)	.168
C4a, mg/L	11	13.3 (13.6)	14	14.9 (10.4)	10	16 (23.9)	.784
C3c, mg/L	11	689.8 ± 263	14	780.3 ± 231.9	13	793 ± 225.3	.513
Transthyretin, mg/L	18	148 ± 59.3	25	193 ± 95.6	20	149.8 ± 68	.112
α1-Microglobin, mg/L	9	2.68 ± 1.41	11	2.58 ± 0.96	9	2.48 ± 1.27	.193

C3c, Complement fraction C3c; *C4a,* complement fraction C4a; *C4BP,* complement C4-binding protein; *IQR,* interquartile range; *SD,* standard deviation; *TA,* Takayasu arteritis.

[a]Values of $P < .05$ are statistically significant.

Japanese (24:1), and higher than that of Indian (2.1:1) and Thai (2.15:1) patients.

Second, the aortic arch and its branches (type I) are the most frequently involved vessels, which is in accordance with the results of Korean and Japanese studies. For Indian patients, however, the abdominal aorta or renal arteries, or both (type V and type IV), are affected more commonly.

Finally, laboratory investigations show a significant elevation of ESR and a mild anemia in TA patients, although other items are within normal ranges.[11] Various types of autoantibody found in the circulation of TA patients may accelerate the aging and death of red blood cells and may explain the anemia found in TA patients.

ESR level was significantly elevated in this group of TA patients, especially in the active-phase patients. A literature review found that ESR, one of the most often-used indexes in TA patients, seems to take an "inconsistent" presentation. Hall et al[19] found that ESR was raised in 78% of 32 patients and correlated well with the corticosteroid treatment. Another report from Korea of 108 TA patients showed that 96.7% of patients with active disease had an elevated ESR level compared with 11.8% in those in remission, and the mean ESR level of the active group was significantly higher than that of the inactive group.[20]

Other researchers have drawn a contrary conclusion, however, and the specificity and sensitivity of ESR are suspected. In a study from the NIH, ESR was elevated in almost half of the patients with clinically inactive disease and was within a normal range in 28% of patients with active disease. The authors also found that >40% of the patients who had been believed to be inactive, with a normal ESR before the operation, were ultimately confirmed by histopathology to be in an active disease phase.[21,22]

The data in our study presented a significant elevation of ESR level in active-phase patients compared with inactive-phase patients and controls. When analyzing the data, however, we should not neglect the influencing factor that the participants were assessed and grouped by the NIH criteria, in which an elevation of ESR is considered a criterion. ESR is a nonspecific parameter of inflammation, and is greatly influenced by multiple factors, such as the number, size, and shape of erythrocytes, plasma proteins, and electric charges of the blood cells. It seems that using a single unique serologic marker such as ESR is not sufficient in the monitoring of disease activity.

SAA and C4BP may be supplements to ESR. We found that the circulation levels of SAA and C4BP in active-phase patients were significantly higher than those in inactive-phase patients and in healthy controls, and the levels in the inactive patients were still higher than those of the controls. These data indicate that SAA and C4BP may be helpful in the assessment of disease activity in TA patients.

SAA is the most sensitive acute-phase protein. It has been reported to be a valuable marker in activity monitoring in inflammatory diseases such as arthritis and pancreatitis. SAA rapidly responds to inflammatory stimulus with a dramatic increase in plasma concentration, sometimes approaching 1000-fold. Our data did not show such a great difference between groups, but they varied considerably among individual patients.

Production of SAA in hepatocytes is mainly regulated by cytokines such as interleukin-6, interleukin-1, and tumor necrosis factor-α. Meanwhile, these cytokines have been verified to be major members of the complicated inflammatory factor nets in the pathogenesis of TA. This may partially explain the elevation of SAA in TA patients. SAA is also a modulator of immune inflammatory reactions. In vitro studies indicate that SAA promotes adhesion, migration, and infiltration of lymphocytes and monocytes, regulates production of cytokines by inflammatory cells, and increases the generation of extracellular matrix metalloproteinases.[23,24] So, SAA may participate in the damage reaction of the artery wall.

C4BP is a high-molecular-weight plasma glycoprotein structurally composed of six or seven identical α-chains and

one or no β-chain. The plasma level of C4BP increases up to fourfold in immune-mediated diseases such as systemic lupus erythematosus, nephrotic syndrome, solid tumors, and acute pneumonia. C4BP is synthesized in liver cells, also under the regulation of proinflammatory factors. Multifunction of C4BP has been found, including inhibiting the activation of classical and lectin pathway of complements, modulating anticoagulation activity of protein S, and sustaining the survival of B lymphocytes. The function and significance of C4BP in the pathogenesis of TA patients is waiting for further study.

CRP is not a reliable index for activity assessment in TA patients according to our data, a conclusion that is also supported by previous studies.[25,26] Other acute-phase proteins tested in this study, including fibrinogen, SAP, haptoglobin, transthyretin, AAG, AMG, C3c, and C4a did not show activity-correlating alterations in the plasma levels. However, considering this is a trans-section study at a single point of time, we could not rule out the possibility that these acute-phase proteins can be used as a biomarker longitudinally in individual patients.

A primary limitation of this study is that used a scoring system to identify disease activity instead of the gold standard of histopathology. This was because obtaining pathologic specimens from TA patients is impractical in most cases. Another limitation is that six patients of the active-phase group were receiving immunosuppressive therapy when the blood samples were collected, and these agents might have an influence on the synthesis of proteins in hepatocytes.

CONCLUSIONS

We examined the plasma concentrations of 11 kinds of acute-phase proteins in TA patients in different phases of disease activity and in controls. To the best of our knowledge, this is the first study to characterize circulating acute-phase proteins rather than only ESR and CRP in a cohort of TA patients. The levels of SAA and C4BP in active-phase patients were significantly higher than those in inactive-phase patients and controls. The levels in inactive TA patients are still higher than that of controls. SAA and C4BP may be useful for the diagnosis and activity discrimination of patients with TA. These results are still waiting for further testing by a larger group of patients in longitudinal manner.

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AUTHOR CONTRIBUTIONS

Conception and design: WQ, MJ, LX, CZ
Analysis and interpretation: WQ, MJ, LX, KL, WH
Data collection: MJ, LX, CZ, KL, WH
Writing the article: MJ
Critical revision of the article: WQ, LX, CZ
Final approval of the article: WQ, CZ
Statistical analysis: MJ, LX
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Overall responsibility: WQ

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