Plasma pentraxin-3 levels in patients with Takayasu's arteritis during routine follow-up

F. Alibaz-Oner[1], K. Aksu[2], S.P. Yentur[3], G. Keser[2], G. Saruhan-Direskeneli[3], H. Direskeneli[1]

[1]Marmara University, School of Medicine, Division of Rheumatology, Istanbul, Turkey;
[2]Ege University, School of Medicine, Division of Rheumatology, Izmir, Turkey;
[3]Istanbul University, Istanbul Medical Faculty, Department of Physiology, Istanbul, Turkey.

Fatma Alibaz-Oner, MD
Kenan Aksu, MD, Prof.
Sibel P. Yentur, PhD
Gökhan Keser, MD, Prof.
Güher Saruhan-Direskeneli, MD, Prof.
Haner Direskeneli, MD, Prof.

Please address correspondance to:
Dr Fatma Alibaz-Oner,
Rheumatology Department,
Marmara University,
School of Medicine,
Fevzi Çakmak Mahallesi 1121,
Sokak 14, Esenler,
34200 Istanbul, Turkey.
E-mail: falibaz@gmail.com

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ABSTRACT

Objective. *To date, no biomarker is universally accepted to be a surrogate for active disease being one of major difficulties in follow-up of Takayasu's arteritis (TAK). In this study, we aimed to investigate plasma pentraxin-3 (PTX-3) levels and its correlation with activity in patients with TAK.*

Methods. *This cross-sectional study included 94 patients (age: 43.3±13.6 years, F/M: 80/14) with TAK, 40 age-sex matched control donors (age: 41.5±9.3 years, F/M: 28/12). TAK patients were evaluated by physician's global assessment (PGA; active/inactive), as well as with the activity definition by Kerr et al. and with a new composite index of ITAS2010 (Indian Takayasu Clinical Activity Score). Plasma PTX-3 levels are measured with an enzyme linked immunosorbent assay kit.*

Results. *Thirty-three (35.5%) patients were clinically active with PGA, while 25 (31.6%) patients and 28 (31.8%) patients were accepted to have active disease according to Kerr activity criteria and ITAS2010, respectively. Plasma PTX-3 levels were significantly higher in TAK patients compared to healthy controls (3.5±2.5 ng/ml vs. 2.5±1.6 ng/ml, p=0.029). However, PTX-3 levels were similar among active and inactive patients according to all three assessment tools. PTX-3 levels significantly correlated only with serum CRP levels.*

Conclusion. *Although plasma PTX-3 levels were higher in patients with TAK compared to healthy controls, we observed no association with disease activity, limiting the role of PTX-3 level as a biomarker for active disease in TAK.*

Introduction

Takayasu's arteritis (TAK) is a rare, systemic large-vessel vasculitis that predominantly affects aorta and its major branches (1, 2). The etiopathogenesis of the disease is still unknown, but infectious agents (3) and genetic factors are implicated (4, 5). Assessment of disease activity is still a challenge in TAK and there is no universally accepted biomarker for activity (6). Acute-phase response (APR) (erythrocyte sedimentation rate (ESR) and C-reactive protein(CRP)) is frequently used for disease assessment in TAK, despite being shown to be neither sensitive nor specific enough to monitor disease activity (7).

The first definition of clinical activity in TAK was reported in a study from the National Institute of Health by Kerr *et al.* (presence of constitutional symptoms, new bruits, acute-phase response, or new angiographic features) (8). Although designed to apply to all vasculitides, the Birmingham Vasculitis Activity Score (BVAS) is mostly used in therapeutic trials of ANCA-associated vasculitis and is validated for use in small- and medium-vessel vasculitis. Because, most of the 11 organ systems in BVAS are not involved in TAK (9). Recently, Misra *et. al.* developed and validated the new composite index of ITAS2010 (Indian Takayasu Clinical Activity Score) for the clinical assessment of TAK. The items of ITAS2010 directly related to large arterial disease (*e.g.* stenosis and claudication) are weighted for scoring than general items of disease (*e.g.* fever, fatigue), aiming to give a more detailed perception of the cardiovascular findings (10). In a recent study, we reported that ITAS2010 was discriminatory for activity during the follow up in TAK. The total agreement between ITAS2010 and Kerr *et al.* was 86.5% (11).

Pentraxin (PTX) superfamily is a group of proteins recognising a wide range of exogenous pathogenic substances and behaving as APR mediators (12).

They are categorised as short and long pentraxins according to their primary structure. CRP and serum amyloid P are classic short pentraxins produced in the liver. PTX-3 is a prototype of the long pentraxins, released especially by dendritic cells, macrophages and vascular cells in response to proinflammatory signals (13, 14). Increased PTX-3 levels were observed in inflammatory rheumatological diseases such as systemic lupus erythematosus (15), rheumatoid arthritis (16) and vasculitides such as and giant cell arteritis (17). Recently, PTX-3 was suggested as a biomarker for disease activity in patients with TAK (18, 19). In this study, we aimed to investigate plasma PTX-3 levels and its association with clinical activity in Turkish patients with TAK during routine follow-up, to validate these observations.

Methods

This cross-sectional study included 94 patients (age: 43.3±13.6 years, F/M: 80/14) with TAK and 40 age and sex-matched healthy controls (age: 41.5±9.3 years, F/M: 28/12). All patients with TAK fulfilled the criteria of American College of Rheumatology (ACR) and evaluated during their routine follow-up visits (20). According to the angiographic classification, 43.1% (n=40) of the study group had type I, 40.8% (n=38) had type V, 4.3% (n=4) had type IV, 8.6% (n=8) had type IIb and 1.1% (n=1) had type III disease (21). Sixty-two patients (66.7%) were on oral corticosteroid (CS) therapy. While only 7 patients were medium or high-dose corticosteroids (≥10 mg), 55 patients were on low-dose corticosteroids (<10 mg). With respect to immunosuppressive (IS) agents, 44 (47.3%) patients were on azathioprine, 32 (34.4%) were on methotrexate, 7 (7.5%) were on leflunomide and single patients (1.1%) each on leflunomide plus methotrexate and leflunomide plus infliximab therapies.

TAK patients were evaluated by physician's global assessment (PGA: active/inactive) and according to the definition of activity by Kerr *et al*. (if available) (8). We also used ITAS2010 and ITAS-A(calculated combining ITAS2010 score with APR (ESR or CRP), as suggested). ITAS-ESR was calculated as ITAS plus 0 for <20, 1 for 21-39, 2 for 40-59 and 3 for >60 mm/hour of ESR by Westergren method. ITAS-CRP was calculated as ITAS plus 0 for=<5, 1 for 6-10, 2 for 11-20 and 3 for >20 mg/L. If both ITAS-ESR and ITAS-CRP were available, the higher score was accepted as ITAS-A. Active disease was defined as >1 for ITAS2010 and >4 for ITAS-A subsets (10).

Plasma were separated from venous blood specimens and stored at -80°C until assayed. Commercial enzyme linked immunosorbent assay (ELISA) kits were used to measure plasma PTX-3 levels (Hycult Biotech, Netherlands). ESR (modified Westergren method) and CRP levels were measured at the same time of the collection of plasma samples. Imaging modalities available during the visits were recorded. Positive imaging was defined as development of a new vascular involvement or progression in luminal vascular lesions. The study was performed according to the Declaration of Helsinki, all subjects gave informed consent before participation. The study was approved by the local ethics committee of Marmara University, School of Medicine. Statistical data were analysed with Statistical Package for the Social Sciences 16.0 (SPSS, Chicago, IL, USA) programme. Results were expressed as means and standard deviations or as median (minimum-maximum) according to the distribution of data. The independent-samples *t*-test, Kruskal-Wallis and chi-square test were used for comparisons. Pearson correlation test was used to analyse correlations.

Table I. Plasma pentraxin-3 levels according to different activity assessment tools.

		Plasma pentraxin-3 level (ng/ml)	*p*-value
PGA	Active	3.2 ± 2.4	0.442
	Inactive	3.6 ± 2.4	
Activity by Kerr *et al*.	Active	3.7 ± 2.2	0.981
	Inactive	3.6 ± 2.5	
ITAS2010	Active	3.9 ± 2.5	0.214
	Inactive	3.3 ± 2.3	
ITAS-A	Active	4.2 ± 2.6	0.147
	Inactive	3.3 ± 2.3	

PGA: Physician's global assessment; ITAS: Indian Takayasu Clinical Activity Score.

Results

Mean disease duration was 6.8±7.2 (0-42) years. Mean ESR was 24±17 mm/h and median CRP level was 4.9 mg/L (0.3-63.8). Thirty-three (35.5%) patients were clinically active according to PGA, 25 (31.6%)(n=79) were active as defined by Kerr *et al*. and 28 (31.8%) were active according to ITAS2010 (n=88).

Plasma PTX-3 levels were significantly higher in TAK compared to healthy controls (3.5±2.5 ng/ml vs. 2.5±1.6 ng/ml, p=0.029). However, PTX-3 levels were observed to be similar in both active and inactive patients, when defined by any assessment tool (PGA, Kerr *et al*. or ITAS2010) (Table I). PTX-3 levels associated significantly with CRP (r=0.236, p=0.025) and ITAS2010 score (r=0.226, p=0.034).

There were no associations between PTX-3 and ESR, age, gender and disease duration. PTX-3 levels were similar in patients with and without concurrent CS therapy (p=0.869). PTX-3 levels were also similar between patients taking azathioprine, methotrexate or leflunomide (p=0.307). Imaging modalities were available in 35 patients during their regular visits. In 16 (45.7%) of these, a new lesion or a radiologic progression in at least one vessel was detected. PTX-3 levels were also similar in patients developing radiologic progression or not (p=0.487).

Discussion

Assessment of activity is still a big challenge in the follow-up of TAK. Serum biomarkers such as interleukin (IL)-6, IL-8, IL-12 and IL-18 (22-25)

and matrix metalloproteinase-9 (15) have been suggested to be associated with active disease in a few studies. Recently, we have also observed significantly increased IL-6, IL-8 and IL-18 levels in patients with TAK, however only IL-18 levels were associated with active disease asassessed by ITAS2010. IL-18 was the only cytokinecorrelating with CRP (26).

In this study, although plasma PTX-3 levels were significantly higher in TAK patients, we could not demonstrate an association with active disease defined by any assessment tool (PGA, Kerr *et al*. or ITAS2010). Previously, higher PTX-3 levels were reported in patients with active TAK compared to inactive patients with infections and healthy controls (14). Ishihara *et al*. similarly showed significantly increased PTX-3 levels in active TAK patients when assessed by Kerr *et al*. When serial assessments were performed with PTX-3 and CRP, although serum CRP levels were negative throughout the course (with only one exception), PTX-3 levels were above the average of the normal controls in all samples (15). Ishihara *et al*. also reported that PTX-3 levels were not affected by prednisolone therapy (15).

In a recent study, Tombetti *et al*. again showed increased PTX-3 levels in TAK. In this study, only CRP was higher in active disease and PTX-3 levels were similar between active and inactive patients (assessed by Kerr *et al*.), similar to our results. As a new observation, Tombetti *et al*. observed significantly higher PTX-3 levels in patients showing 'detectable signs of vascular inflammation' by vascular imaging, while CRP levels (although numerically higher) were reported to be similar (27). However, number of patients with active imaging was quite low to reach a definite conclusion in this study. Similarly, number of patients in our study with vascular imaging was not sufficient to support this observation. However, not supportive of this claim, we recently have observed that 18-fluorodeoxyglucose positron emission tomography scanning was positive with increased uptake in most TAK patients with an elevated APR (either ESR or CRP) but no symptoms or signs of active disease (28).

The major limitation of our study is its cross-sectional nature. High proportion use of IS therapies including CS is another limitation. However, we still think that our results are useful and show the limitations of current biomarker evaluation in TAK, which,as a slowly progressive disease, has a limited inflammatory response during routine follow-up.

In conclusion, plasma PTX-3 levels were found to be significantly higher in TAK compared to healthy controls. But PTX-3 levels were similar in active and inactive patients when assessed according to various activity assessment tools. Therefore, our results do not support previous observations that plasma PTX-3 levels may be a discriminatory biomarker for active disease in TAK. There seems to be a need for prospective follow-up studies with PTX-3 as a biomarker in TAK, including also more patients with vascular progression as well as with active disease.

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