Journal of the American College of Cardiology Vol. 57, No. 16, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00

CORRESPONDENCE

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Sensitive Assessment of Activity of Takayasu's Arteritis by Pentraxin3, a New Biomarker

To the Editor: Takayasu's arteritis (TA) is a chronic vasculitis mainly involving the aorta and its main branches (1). The erythrocyte sedimentation rate and C-reactive protein (CRP) level have generally been used to monitor disease activity. In addition to steroids and conventional immunosuppressants, new agents are reported to be very effective for patients who are resistant to steroids and other drugs (2). We occasionally experience patients with inflammatory symptoms but without a significant increase in CRP. It is often difficult to identify patients in whom a recurrence develops after treatment with steroids and other immunosuppressant drugs using conventional imaging tests and biomarkers. Therefore, we need sensitive biomarkers to assess subtle TA activity.

Pentraxins are a superfamily of conserved proteins characterized by the pentraxin domain. CRP is recognized as a classic short pentraxin, whereas pentraxin3 (PTX3) belongs to the long pentraxins. PTX3 is produced locally by a variety of tissues and cells, such as vascular endothelial cells, macrophages, and neutrophils, predominantly in response to proinflammatory signals.

Matrix metalloproteinases (MMPs) are a group of >20 zinc-containing endopeptidases that are either secreted or expressed at the cell surface of all main vascular cell types. These proteinases degrade interstitial tissues during the process of vessel inflammation and repair.

We hypothesized that serum PTX3 and MMP levels could be sensitive biomarkers of TA activity to detect patients in whom a recurrence develops, even in the absence of an increase in CRP.

We screened 41 consecutive patients (2 males and 39 females aged 13 to 49 years; average, 31.9 years) with a diagnosis of TA. The diagnosis was based on the presence of symptoms and signs of ischemic and inflammatory large-vessel disease supported by magnetic resonance angiography (MRA). All patients fulfilled >3 of the 1990 American College of Rheumatology criteria for TA classification (3). According to the patient clinical symptoms, 23 patients were classified as in the active phase (2 males and 21 females aged 13 to 47 years; average, 27.5 years) as evidenced by clinical recurrences such as progression of arterial stenosis or dilation on MRA and carotid artery ultrasound, worsening numbness of the arms, continuous fever, arm pain with use, or neck or jaw pain within 2 years of blood sampling. These clinical signs and symptoms were usually accompanied by an increase in the serum CRP level, but some patients did not show an increase >0.5 mg/dl. Febrile patients with apparent causes were not considered as having a TA recurrence. All patients in this group satisfied the National Institutes of Health criteria for active TA disease (4). Eighteen patients were categorized as in the inactive phase (all were females aged 25 to 49 years; average, 37.6 years). Twenty healthy subjects (all were females age 19 to 45 years; average 30.3 years) were registered as normal controls.

Circulating levels of high-sensitivity C-reactive protein (hsCRP), PTX3, MMP-2, and MMP-3 were determined by enzyme-linked immunosorbent assay. Patients in the active phase had significantly higher levels of PTX3 than those in the inactive phase and controls. There were no differences among the groups in serum hsCRP, MMP-2, and MMP-3 levels (Fig. 1). Using the receiver-operating characteristic curve, we determined the cutoff values (hsCRP >1,734 ng/ml, PTX3 >5.37 ng/ml) to determine the sensitivity (SE), specificity (SP), and the area under the receiver-operating characteristic curve (hsCRP: SE 65.2%, SP 94.4%; area under the curve 0.905; PTX3: SE 82.6%, SP 77.8%, area under the curve 0.914).

Eight of 23 patients in the active phase had a negative hsCRP level (<1,734 ng/ml). Among these patients, we determined the SP and SE of PTX3 (SE 75.0%, SP 76.5%). The PTX3 level was increased in 6 of the 8 patients.

We examined the relationship between the prednisolone dose and each biomarker. We found that there was a positive correlation between the plasma MMP-3 level and the prednisolone dose. However, PTX3 levels were not correlated with prednisolone dose (MMP-3: $R = 0.649$; PTX3: $R = 0.432$).

PTX3 is more specific for arterial inflammation than CRP because of the mechanism of induction and location of production. We performed immunohistochemical staining of the aortic aneurysm from patients with TA after surgery. Endothelial cells of the vasa vasorum and inflammatory cells were positive for PTX3. One of the histological features of TA is hyperplasia of vasa vasorum. Therefore, it is reasonable that PTX3 is increased in the blood in response to subtle vascular inflammation; however, further studies are needed to investigate this.

The mechanisms by which steroids increase MMP-3 serum levels remain unknown. However, determining the MMP-3 level to assess TA disease activity should be done with caution. In contrast, PTX3 level is not affected by prednisolone. Considering the need for prednisolone in patients with TA, this evidence is very important for assessing TA activity.

There are limitations to this study. The size of this study is small, and the length of follow-up for these patients might not be sufficiently long. More importantly, the relationship between the long- or mid-term prognosis and the levels of these biomarkers should be a subject of investigation, although it takes many years.

We conclude that PTX3 could be a new and sensitive biomarker to assess TA activity, which is not affected by prednisolone. Moreover, this study could help to establish new and more accurate criteria for assessing TA activity than National Institutes of Health criteria, which are the only criteria that we could use.

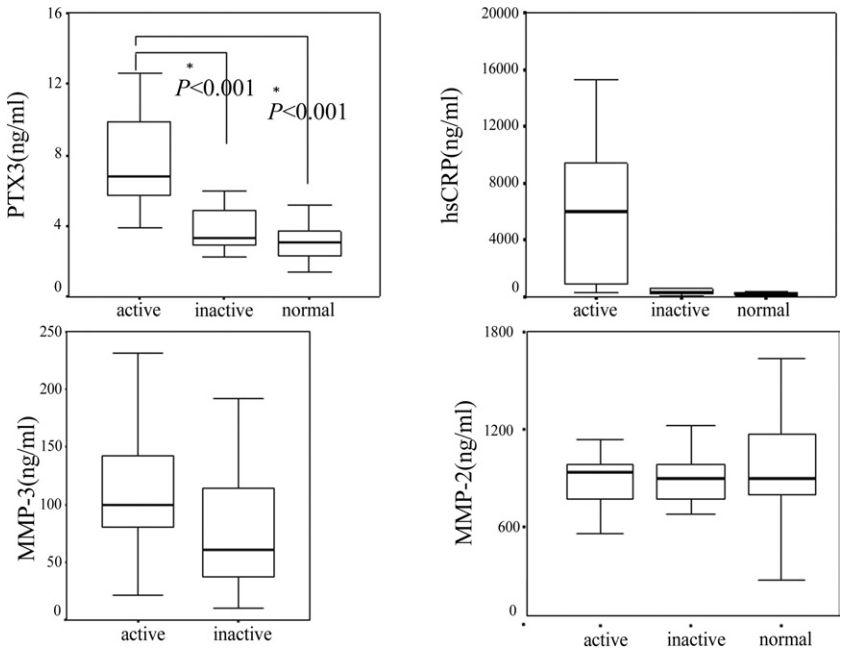

Figure 1 Serum Levels of hsCRP, PTX3, MMP-3, and MMP-2 in Takayasu's Arteritis Patients

*According to 1-way analysis of variance with Games-Howel adjustment. p values <0.05 were considered significant (active, n = 23; inactive, n = 18; normal, n = 20). hsCRP = high-sensitive C-reactive protein; MMP = matrix metalloproteinase; PTX3 = pentraxin 3.

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doi:10.1016/j.jacc.2010.10.058

Please note: Supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Health, Labour, and Welfare. The sponsor of the study had no direct role in the study design, data collection, data analysis, data interpretation, or writing of the report.

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Letters to the Editor

Procedure Volume and Outcome
You Should Take Into Account Each Hospital

We read with interest the article by Freeman et al. (1). The authors investigated the relationship between hospital implantable cardioverter-defibrillator (ICD) implantation volume and procedural complications.

They found that patients who have an ICD implanted at a high-volume hospital are less likely to have an adverse event associated with the procedure; patient data were collected from 1,201 different hospitals. An appropriate statistical method is critical when investigating the impact of procedure volume on clinical outcome. One-level hierarchical logistic regression to