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Circulating cold-inducible RNA-binding protein levels in microscopic polyangiitis and granulomatosis with polyangiitis

Correlation with disease activity

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Abstract

Objective: This study investigated whether circulating cold-inducible RNA-binding protein (CIRP) could be a biomarker to reflect the current activity, function, and damage status in patients with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA).

Methods: This study selected 39 MPA and 26 GPA patients. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)-specific indices include the Birmingham Vasculitis Activity Index (BVAS), five-factor score (FFS), the Korean version of the Short-Form 36-Item Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS), and the vasculitis damage index (VDI). The highest tertile of BVAS was defined as high activity of AAV.

Results: The median age of the study subjects was 65.0 years and 53.8% were women. The median BVAS, FFS, SF-36 PCS, MCS, and VDI scores were 12.0, 2.0, 47.5, 50.3, and 3.0, respectively. The median circulating CIRP level was 6.4 ng/mL. Among the four AAV-specific indices, circulating CIRP was significantly correlated with BVAS ($r = 0.256$). Using the receiver operator characteristic curve, the cut-off of circulating CIRP for high activity of AAV was 6.16 ng/mL. High activity of AAV was identified more frequently in patients with circulating CIRP ≥ 6.16 ng/mL than in those with circulating CIRP < 6.16 ng/mL (48.6% vs. 21.4%). In addition, patients with circulating CIRP ≥ 6.16 ng/mL exhibited a significantly higher risk for high activity of AAV than those with circulating CIRP < 6.16 ng/mL (relative risk 3.474).

Conclusion: This study suggests the clinical potential of circulating CIRP as a biomarker for reflecting the current BVAS and predicting high activity of AAV in patients with MPA and GPA.

Keywords

ANCA · Vasculitis · Biomarker · Severity · BVAS

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Co-first authors: Taejun Yoon and Jang Woo Ha contributed equally to this work.

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Introduction

Cold-inducible RNA-binding protein (CIRP) is a universal stress-response protein, and its expression may be regulated by hypoxia, ultraviolet radiation, glucose starvation, and oxygen radicals in addition to cold shock [1]. Intracellular CIRP may play an important role in anti-apoptotic processes and cell protection in response to stress through stabilizing mRNAs and facilitating their translation [2]. Concurrently, secreted extracellular CIRP (circulating CIRP) participates in the proinflammatory process via Toll-like receptor 4/myeloid differentiation 2 (TLR4/MD2)-mediated and triggering receptor expressed on myeloid cell-1 (TREM-1)-mediated intracellular inflammatory signaling [3]. To date, roles of circulating CIRP in various inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, sepsis, acute lung injury, and cardiac ischemia have been reported [4]. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a representative small-vessel vasculitis with histopathological features exhibiting necrotizing vasculitis affecting mainly small-sized vessels including capillaries, adjacent arterioles, and venules. In addition, AAV may occasionally initiate inflammatory processes in medium-sized arteries [5, 6]. It can be assumed that circulating CIRP may be associated with the activity, function, and damage status of AAV, given that TLR4 and TREM-1 have been reported to be involved in the pathogenesis of AAV [7, 8]. However, there have been no studies on the clinical role of circulating CIRP in patients with AAV to date. Hence, this study investigated whether circulating CIRP could be a biomarker to reflect the current activity, function, and damage status in patients with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA).

Materials and methods

Study population

This study selected 65 microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) patients who met the inclusion criteria described below from the Severance Hospital ANCA-Associated

Vasculitides (SHAVE) cohort (a prospective observational cohort of patients with MPA, GPA, and (eosinophilic granulomatosis with polyangiitis) EGPA). The inclusion criteria were as follows: i) the first classification of MPA and GPA at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, and Severance Hospital; ii) fulfilment of both the 2007 European Medicines Agency algorithms for AAV and polyarteritis nodosa, and the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [5, 6]; iii) reclassified as having MPA and GPA according to the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for MPA and GPA [9, 10]; iv) well-documented medical records regarding clinical and laboratory data at diagnosis including AAV subtype, ANCA positivity, AAV-specific indices, the systemic items belonging to Birmingham Vasculitis Activity Score (BVAS), and routine laboratory results; v) absence of serious medical conditions such as malignancies, infectious diseases requiring hospitalization, and systemic and autoimmune diseases other than AAV; and vi) no exposure to glucocorticoids more than 20 mg/day or immunosuppressive drugs for AAV treatment within the first year prior to AAV diagnosis. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2016-0901) and, when required, written informed consent was obtained from patients at the time of blood sampling. The IRB waived the need for written informed consent when it had been previously obtained at entry into the SHAVE cohort.

AAV-specific indices and blood collection

AAV-specific indices include BVAS version 3 [11], five-factor score (FFS) [12], the Korean version of the Short-Form 36-Item Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS) [13], and the vasculitis damage index (VDI) [14]. Whole blood was obtained from patients who provided consent on the same day that the assess-

ments of AAV-specific indices were completed. Serum was immediately isolated from whole blood and stored at -80°C . In this study, AAV-specific indices and serum stored at AAV diagnosis were used.

Clinical and laboratory data

Clinical and laboratory data were collected as described in [Table 1](#). The titers of myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA were measured using an immunoassay, the novel anchor-coated highly sensitive (hs) Phadia ELiA (ThermoFisher Scientific/Phadia, Freiburg, Germany) and human native antigens, on the Phadia250 analyzer. An immunoassay for MPO-ANCA and PR3-ANCA is recommended as the first screening method for ANCA [15]; however, perinuclear (P)-ANCA or cytoplasmic (C)-ANCA positivity was also accepted as ANCA positivity according to the 2022 ACR/EULAR classification criteria for MPA and GPA [9, 10].

High activity of AAV

The highest tertile of BVAS was defined as high activity of AAV.

Measurement of circulating CIRP

Circulating CIRP was quantified in stored sera using enzyme-linked immunosorbent assay kits (MBL, Nagoya, Japan) according to the manufacturer's instructions.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians with interquartile ranges, whereas categorical variables were expressed as numbers (percentages). The correlation coefficient (r) between the two variables was obtained using Pearson correlation analysis. The significant area under the curve (AUC) was confirmed and the optimal cut-off was extrapolated by performing a receiver operator characteristic (ROC) curve analysis. The value of circulating CIRP with the maximized sum of sensitivity and specificity for the lower limit of the highest tertile of BVAS was selected

Table 1 Characteristics of patients (N=65)	
Variables	Values
<i>Demographic data</i>	
Age (years)	65.0 (19.0)
Female gender, N (%)	35 (53.8)
<i>AAV subtypes, N (%)</i>	
MPA	39 (60.0)
GPA	26 (40.0)
<i>ANCA positivity, N (%)</i>	
MPO-ANCA (or P-ANCA) positive	47 (72.3)
PR3-ANCA (or C-ANCA) positive	13 (20.0)
<i>AAV-specific indices</i>	
BVAS	12.0 (11.0)
FFS	2.0 (1.0)
SF-36 PCS	47.5 (37.3)
SF-36 MCS	50.3 (32.0)
VDI	3.0 (2.0)
<i>Systemic items of BVAS, N (%)</i>	
General manifestation	24 (36.9)
Cutaneous manifestation	9 (13.8)
Mucous and ocular manifestation	3 (4.6)
Otorhinolaryngologic manifestation	21 (32.3)
Pulmonary manifestation	43 (66.2)
Cardiovascular manifestation	5 (7.7)
Gastrointestinal manifestation	1 (1.5)
Renal manifestation	40 (61.5)
Nervous systemic manifestation	14 (21.5)
<i>Laboratory results</i>	
White blood cell count (/mm ³)	8640.0 (6750.0)
Hemoglobin (g/dL)	10.6 (3.7)
Platelet count (× 1000/mm ³)	281.0 (167.0)
Total protein (g/dL)	6.5 (1.1)
Serum albumin (g/dL)	3.6 (1.2)
Blood urea nitrogen (mg/dL)	22.8 (21.3)
Serum creatinine (mg/dL)	0.9 (1.2)
ESR (mm/h)	57.0 (83.0)
CRP (mg/L)	7.0 (59.2)
Circulating C1RP (ng/mL)	6.4 (3.8)
Values are expressed as a median (interquartile range) or N (%)	
ANCA antineutrophil cytoplasmic antibody, AAV ANCA-associated vasculitis, MPA microscopic polyangiitis, GPA granulomatosis with polyangiitis, MPO myeloperoxidase, P perinuclear, PR3 proteinase 3, C cytoplasmic, BVAS Birmingham Vasculitis Activity Score, FFS five-factor score, SF36 36-item short form survey, PCS physical component summary, MCS mental component summary, VDI vasculitis damage index, ESR erythrocyte sedimentation rate, CRP C-reactive protein, C1RP cold-inducible RNA-binding protein	

as its cut-off for high activity of AAV. The relative risk (RR) of the cut-off for high activity of AAV was analyzed using contingency tables and the chi-square test. *P*-values ≤ 0.05 were considered statistically significant.

Results

Characteristics

The median age of the study subjects was 65.0 years and 53.8% were women. Among the 65 patients, 39 and 26 had MPA and GPA, respectively. MPO-ANCA (or P-ANCA)

and PR3-ANCA (or C-ANCA) were positive in 47 and 13 patients, respectively. The median BVAS, FFS, SF-36 PCS, MCS, and VDI scores were 12.0, 2.0, 47.5, 50.3, and 3.0, respectively. The most common systemic item defined by the form of BVAS was pulmonary manifestation (66.2%), followed by renal manifestation (61.5%). Median erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and circulating C1RP were 57.0 mm/h, 7.0 mg/L, and 6.4 ng/mL, respectively (Table 1).

Correlations

Circulating C1RP was significantly correlated with BVAS ($r = 0.256$, $P = 0.039$). However, circulating C1RP was not correlated with other AAV-specific indices or acute-phase reactants, including ESR and CRP (Fig. 1).

Cut-off and relative risk

Using the ROC curve, the cut-off of circulating C1RP for high activity of AAV was 6.16 ng/mL; the sensitivity and specificity were 75.0 and 53.7%, respectively. When patients were divided into two groups according to circulating C1RP ≥ 6.16 ng/mL, 37 of the 65 patients were assigned to the group with circulating C1RP ≥ 6.16 ng/mL. High activity of AAV was identified more frequently in patients with circulating C1RP ≥ 6.16 ng/mL than in those with circulating C1RP < 6.16 ng/mL (48.6% vs. 21.4%, $P = 0.024$). In addition, patients with circulating C1RP ≥ 6.16 ng/mL exhibited a significantly higher risk for high activity of AAV than those with circulating C1RP < 6.16 ng/mL (RR 3.474, 95% confidence interval 1.146, 10.533; Fig. 2).

Discussion

This study is the first to demonstrate that circulating C1RP could reflect the current BVAS and predict high activity of AAV in patients with MPA and GPA. However, circulating C1RP was not significantly correlated with other AAV-specific indices or acute-phase reactants, whereas BVAS was significantly correlated with SF-36 PCS ($r = -0.340$, $P = 0.006$), SF-36 MCS ($r = -0.344$, $P = 0.05$), ESR ($r = 0.472$, $P < 0.001$), and CRP ($r = 0.342$, $P = 0.005$).

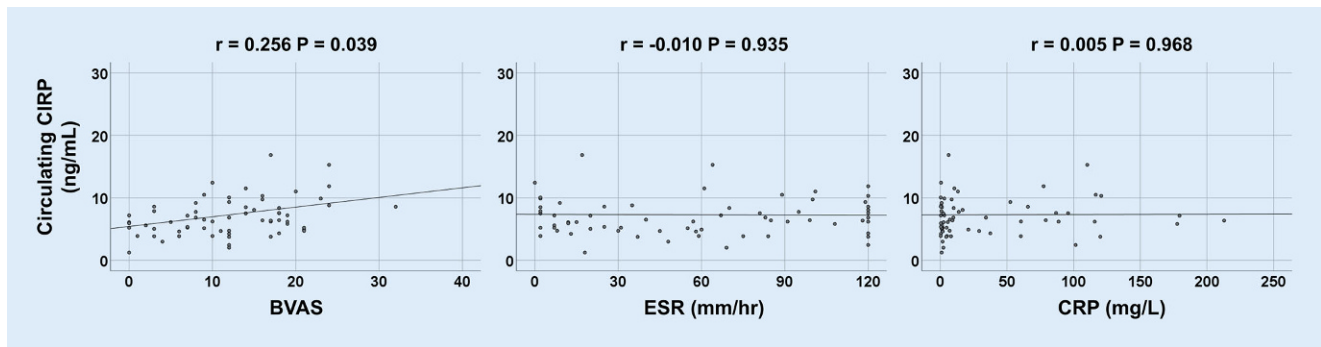


Fig. 1 ▲ Correlation analyses of circulating C1RP with the current BVAS, ESR, and CRP. C1RP cold-inducible RNA-binding protein, BVAS Birmingham Vasculitis Activity Score, ESR erythrocyte sedimentation rate, CRP C-reactive protein

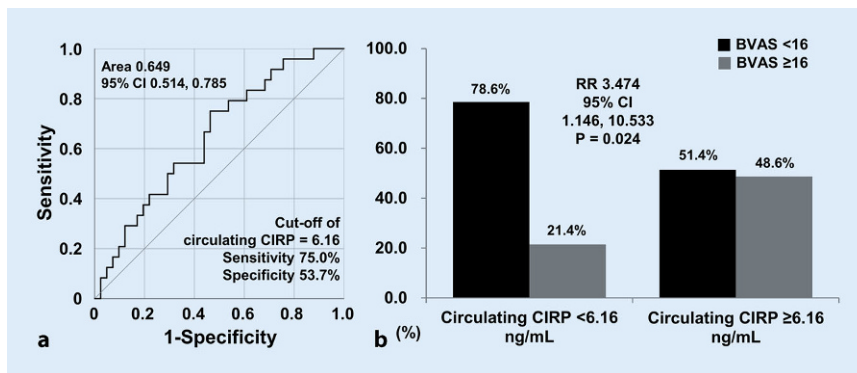


Fig. 2 ▲ ROC curve and relative risk. a) ROC curve of circulating C1RP based on high activity of AAV (BVAS ≥ 16), b) Relative risk of the cut-off of C1RP for high activity of AAV (BVAS ≥ 16). ROC receiver operator characteristic, C1RP cold-inducible RNA-binding protein, AAV antineutrophil cytoplasmic antibody-associated vasculitis, BVAS Birmingham vasculitis activity score

These results suggest that circulating C1RP reflects BVAS through rather complex and diverse mechanisms.

This study suggests several possibilities given several shared roles in the inflammatory processes between circulating C1RP and AAV pathophysiology, although the direct mechanism by which circulating C1RP is correlated with BVAS remains uncertain. The first shared mechanism is the upregulated production of various proinflammatory cytokines and chemokines [16]. Circulating C1RP was reported to promote the production of tumor necrosis factor- α , interleukin-1 β , interleukin-6, and C-X-C motif chemokine ligand 2, which initiate and aggravate the inflammatory response and recruit neutrophils into inflamed tissues [17]. These cytokines may play an important role in not only ANCA formation but also in neutrophil priming in AAV pathogenesis [16]. The second shared mechanism is neutrophil extracellular trap (NET) for-

mation [18]. Circulating C1RP has been reported to induce neutrophil extracellular trap (NET) formation in patients with sepsis and acute pancreatitis [19, 20]. Subsequently, circulating C1RP-induced NET formation might deteriorate phagocytic clearance of apoptotic cells by macrophages [21], leading to a vicious circle. The third shared mechanism is endothelial dysfunction [16]. It was reported that circulating C1RP can increase the formation of reactive oxygen species and caspase-1 activation via nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome activation [17, 22]. Based on these shared mechanisms, it was concluded that circulating C1RP has a reasonable background supporting its clinical significance as a biomarker to reflect the activity of MPA and GPA.

This study performed subgroup analyses according to the subtype of AAV, ANCA type, and systemic manifestations based on the items of BVAS, and ob-

tained several interesting findings. First, regarding the subtype of AAV, MPA patients exhibited a significantly higher median circulating C1RP than GPA patients (7.6 ng/mL vs. 5.4 ng/mL, $P = 0.001$). Second, regarding AAV type, circulating C1RP was not significantly correlated with MPO-ANCA or PR3-ANCA titers ($r = 0.183$ and $r = -0.082$, respectively). In addition, no significant differences in circulating C1RP were noted based on the presence of MPO-ANCA (or P-ANCA) or PR3-ANCA (or C-ANCA) positivity. Third, regarding systemic manifestations based on BVAS, circulating C1RP exhibited a significant correlation with the total score of renal manifestation ($r = 0.264$, $P = 0.033$). Concurrently, MPA patients showed renal manifestation more frequently than GPA patients (84.6% vs. 26.9%, $P < 0.001$). Therefore, it was concluded that the subgroup analyses elucidated that circulating C1RP serves as a more significant biomarker in MPA patients through a higher frequency of renal manifestations.

This study has several limitations. Firstly, the size of this study was not large enough to provide potentially reliable information on the clinical significance of C1RP in MPA and GPA patients. Secondly, the results of this study could not be verified in a validation cohort consisting of patients from other hospitals because there is no additional AAV cohort other than our cohort for which clinical data of BVAS, FFS, and SF-36 and blood samples of Korean patients who have been newly diagnosed with AAV are immediately available for use. Thirdly, this study could not provide evidence supporting the hypothetical mechanisms of the correlation

between circulating CIRP and the current BVAS. Lastly, the absence of paired results for the same patients was also a critical limitation. However, this study has clinical implications in that it is the first pilot study to demonstrate the possibility that circulating CIRP could reflect the current activity of MPA and GPA. A prospective future study with more patients, in particular by including patients from other hospitals, will provide serial, dynamic, and reliable data regarding the clinical potential of circulating CIRP in MPA and GPA.

Conclusion

This study suggests the clinical potential of circulating CIRP as a biomarker for reflecting the current BVAS and predicting high activity of AAV in patients with MPA and GPA.

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Zirkulierende kälteinduzierbare RNA-bindende Proteine bei mikroskopischer Polyangiitis und Granulomatose mit Polyangiitis. Korrelation mit der Krankheitsaktivität

Ziel: In der vorliegenden Studie wurde untersucht, ob zirkulierendes kälteinduzierbares RNA-bindendes Protein (CIRP) ein Biomarker sein könnte, der die aktuelle Aktivität, Funktionsfähigkeit und den Schädigungsstatus bei Patienten mit einer mikroskopischen Polyangiitis (MPA) und Granulomatose mit Polyangiitis (GPA) widerspiegelt.

Methoden: Für diese Studie wurden 39 MPA- und 26 GPA-Patienten ausgewählt. Zu den Indizes, die für eine mit antineutrophilen zytoplasmatischen Antikörpern (ANCA-) assoziierte Vaskulitis (AAV)-spezifisch sind, gehören der Birmingham Vasculitis Activity Index (BVAS), Fünf-Faktor-Score (FFS), die koreanische Version des Short-Form 36-Item Health Survey (SF-36) mit seiner körperlichen Komponente („physical component summary“, PCS) und seiner psychischen Komponente („mental component summary“, MCS) und der Vasculitis Damage Index (VDI). Das höchste Terzil des BVAS wurde definiert als höchste Aktivität der AAV.

Ergebnisse: Das Alter der Studienteilnehmer lag im Median bei 65,0 Jahren; 53,8% der Teilnehmer waren Frauen. Die medianen Scores für BVAS, FFS, SF-36 PCS, MCS und VDI betragen 12,0; 2,0; 47,5; 50,3 bzw. 3,0. Der mediane Wert für zirkulierendes CIRP lag bei 6,4 ng/ml. Bei den 4 AAV-spezifischen Indizes war zirkulierendes CIRP signifikant mit dem BVAS korreliert ($r = 0,256$). Unter Verwendung der ROC-Kurve („receiver operator characteristic curve“) betrug der Grenzwert des zirkulierenden CIRP für hohe Aktivität der AAV 6,16 ng/ml. Eine hohe Aktivität der AAV wurde häufiger bei Patienten mit Werten $\geq 6,16$ ng/ml für zirkulierendes CIRP als bei Patienten mit Werten $< 6,16$ ng/ml für zirkulierendes CIRP festgestellt (48,6 vs. 21,4%). Darüber hinaus wiesen Patienten mit Werten $\geq 6,16$ ng/ml für zirkulierendes CIRP ein signifikant höheres Risiko für eine hohe Aktivität der AAV auf als Patienten mit Werten $< 6,16$ ng/ml für zirkulierendes CIRP (relatives Risiko 3,474).

Schlussfolgerung: Die vorliegende Studie liefert Hinweise auf das klinische Potenzial von zirkulierendem CIRP als Biomarker, der den aktuellen BVAS widerspiegelt und eine hohe Aktivität der AAV bei Patienten mit MPA und GPA vorhersagt.

Schlüsselwörter

ANCA · Vaskulitis · Biomarker · Schweregrad · BVAS

Declarations

Conflict of interest. T. Yoon, J.W. Ha, J.Y. Pyo, J.J. Song, Y.-B. Park, S.S. Ahn, and S.-W. Lee declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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