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Interferon-gamma Release Assay Results Are Reliable for Screening for Latent Tuberculosis in Antineutrophil Cytoplasmic Antibody-associated Vasculitis

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Abstract. *Background/Aim: This study investigated a correlation between ex vivo interferon-gamma (IFN)-gamma production using IFN-gamma releasing assay (IGRA) and antineutrophil cytoplasmic antibody-associated vasculitis (AAV) activity assessed by Birmingham vasculitis activity score (BVAS) in AAV patients. Patients and Methods: A total of 113 patients with AAV were consecutively selected from the AAV cohort and their medical records were reviewed. IGRA was performed at AAV diagnosis and before the initiation of glucocorticoids or immunosuppressive drugs for AAV treatment. Results: The median age was 61.8 years and 41.6% of the patients were men. Eighteen, 28, and 67 patients had EGPA, GPA, and MPA, respectively. Eighteen, 84, and 11 patients had positive, negative, and indeterminate results, and the median Nil, tuberculosis antigen, mitogen, and ex vivo IFN-gamma production were 0.1, 0.1, 10.0, and 9.8 IU/ml, respectively. There was no significant correlation between ex vivo IFN-gamma production and BVAS in AAV patients. When AAV patients were divided into two groups according to BVAS of 18, the higher tertile of BVAS, there was no significant difference in ex vivo IFN-gamma production between AAV patients with BVAS ≥18 and those without. In addition, there were no statistically significant correlations between ex vivo IFN-gamma production and BVAS in AAV patients with either indeterminate and negative IGRA results or only negative IGRA results. Conclusion: There is no correlation between ex vivo IFN-gamma production and BVAS. This study provided information on the reliability of the IGRA results for latent tuberculosis screening in AAV patients regardless of the activity of AAV.*

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterised by necrotising vasculitis affecting small- and medium-sized vessels and is composed of three subtypes: eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA) (1, 2). Interferon (IFN)-gamma, which is produced by autoreactive CD4+ T_H1 cells, has been known to participate in effector responses and tissue injury in the pathogenesis of AAV, although to lesser extent than other proinflammatory cytokines such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-1beta, and IL-17 (3-5). In addition to CD4+ T cells, the number of CD3+CD4-CD8- T cells producing IFN-gamma has been reported to be increased in AAV patients (6). Conversely, in a previous study, the intracellular expression of IFN-gamma in CD3+ T cells in patients with remitting AAV was significantly higher than in those with active AAV (7). Therefore, the role of IFN-gamma in the pathogenesis of AAV has not been clearly understood so far, compared to type I interferon or T_H1 and T_H17-related cytokines (8).

The IFN-gamma releasing assay (IGRA), which evaluates the level of *ex vivo* IFN-gamma production by T cells, is widely used in clinical practice as a screening test for latent tuberculosis. In particular, testing for latent tuberculosis

infection is frequently prescribed during the treatment of autoimmune diseases. This is because patients being treated with biological agents are required to undergo tuberculosis prophylaxis treatment. In addition, patients that are expected to be treated with moderate to high doses of glucocorticoids for more than one month can be considered to be treated for latent tuberculosis (9). However, while IGRA is a diagnostic test for evaluating latent tuberculosis, it measures IFN-gamma production, a classical inflammatory cytokine, under *ex vivo* conditions. Therefore, IGRA can also reflect the degree of systemic inflammation in itself, no matter the origin. Indeed, it was previously demonstrated that IGRA results are substantially affected by disease severity in critically ill patients and those with inflammatory bowel disease (10, 11).

Whenever AAV patients are enrolled in the Severance Hospital ANCA-associated Vasculitides (SHAVE) cohort, which is an observational cohort of AAV patients, IGRA is usually performed to screen for latent tuberculosis. However, a dysregulation of *ex vivo* production of IFN-gamma occurs in patients with systemic lupus erythematosus, as we have reported using IGRA (12). Hence, this study attempted to investigate whether the levels of *ex vivo* IFN-gamma production measured using IGRA are correlated with AAV activity in AAV patients and inquire into the reliability of IGRA results for screening for latent tuberculosis.

Patients and Methods

Patients. A total of 113 patients with AAV were consecutively selected from the SHAVE cohort according to the following inclusion criteria: i) patients who fulfilled both the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and the 2007 consensus methodology for the classification of AAV (1, 2), which are essential for the inclusion of AAV patients in the SHAVE cohort; ii) patients who had sufficient electronic medical records to collect clinical, laboratory, radiological and histopathological data at AAV diagnosis; iii) patients who had IGRA results at AAV diagnosis but did not have medical histories of pulmonary or extra-pulmonary tuberculosis or any evidence of latent tuberculosis before AAV diagnosis; iv) patients who had no medical conditions affecting AAV diagnosis or the IGRA results such as malignancies, infectious diseases requiring hospitalisation, and immunodeficiency-related disorders at AAV diagnosis; v) patients who had not been exposed to glucocorticoids and immunosuppressive drugs for AAV treatment before the IGRA performance. In all patients included in this study, Birmingham vasculitis activity score (BVAS) and five-factor score (FFS) were assessed at AAV diagnosis (13, 14). This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2016-0901) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of enrolment in the SHAVE cohort and blood sampling.

Clinical data at AAV diagnosis (the IGRA performance). Age, sex, and body mass index were collected as epidemiological data. The AAV subtype, ANCA type and positivity, BVAS, and FFS were obtained as AAV-specific variables. In particular, clinical manifestations were evaluated with reference to BVAS forms (13). Comorbidities included diabetes mellitus, hypertension, and dyslipidaemia. Laboratory results, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were also collected.

Testing for IGRA. Blood samples were drawn to test for IGRA using either the QuantiFERON-TB Gold In-Tube (QFT-GIT) or QuantiFERON-TB Gold PLUS test (QFT-PLUS) (Qiagen, Hilden, Germany), following the instructions provided by the manufacturer. The QFT-GIT test was used at Severance Hospital as an IGRA until September 2018, whereas the QFT-PLUS test was adopted after October 2018. The IGRA results were categorised as negative, positive, or indeterminate, according to the differences in IFN-gamma values in the nil, TB antigen, and mitogen tube, as described elsewhere (12). *Ex vivo* production of IFN-gamma was calculated as the difference in IFN-gamma levels in the mitogen tube and the nil tube.

Statistical analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians (interquartile ranges), whereas categorical variables were expressed as numbers (percentages). The optimal cut-off was extrapolated by performing a receiver operator characteristic (ROC) curve analysis and one value with the maximum sum of sensitivity and specificity was selected. The relative risk (RR) of the cut-off for the high AAV activity was analysed using contingency tables and the chi-square test. Comparison of the cumulative survival rates between the two groups was analysed by the Kaplan-Meier survival analysis with the log-rank test. *p*-Values less than 0.05 were considered statistically significant.

Results

Baseline characteristics. The median age was 61.8 years and 41.6% of the patients were men. Among the 113 patients with AAV, 18, 28, and 67 had EGPA, GPA, and MPA, respectively. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in 75 (66.4%) and 15 (13.3%) patients, respectively, whereas no ANCA was found in 25 (22.1%) patients. The median BVAS, FFS, ESR, and CRP were 14.0, 1.0, 67.5 mm/h, and 20.1 mg/l, respectively. According to the IGRA results, 18 (15.9%), 84 (74.3%) and 11 (9.7%) had positive, negative, and indeterminate results, respectively. As per IFN-gamma levels, the median for nil, tuberculosis antigen, mitogen, and *ex vivo* IFN-gamma production were 0.1, 0.1, 10.0, and 9.8 IU/ml, respectively. The remaining values are presented in Table I.

AAV activity and IFN-gamma production in 113 AAV patients. *Ex vivo* production of IFN-gamma measured by IGRA tended to be inversely correlated with BVAS; however, it did not reach a statistical significance (Figure 1A). In addition, when AAV patients were divided into two groups according to BVAS of 18, the lower limit of the higher tertile of BVAS, 33 (34.7%) patients were assigned to

Table I. *Baseline characteristics of patients with AAV (N=113).*

Variables	Values
Demographic data at AAV diagnosis	
Age (years)	61.8 (20.5)
Male sex [N, (%)]	47 (41.6)
Body mass index (kg/m^2)	22.4 (4.6)
AAV Subtype at AAV diagnosis [N, (%)]	
EGPA	18 (15.9)
GPA	28 (24.8)
MPA	67 (59.3)
ANCA positivity at AAV diagnosis [N, (%)]	
MPO-ANCA (or P-ANCA) positivity	75 (66.4)
PR3-ANCA (or C-ANCA) positivity	15 (13.3)
Both ANCA positivity	2 (1.8)
ANCA negativity	25 (22.1)
AAV-specific indices at AAV diagnosis	
BVAS	14.0 (10.0)
FFS	1.0 (1.0)
Clinical manifestations at AAV diagnosis [N, (%)]	
General	54 (47.8)
Cutaneous	18 (15.9)
Mucous membranous/Ocular	6 (5.3)
Otorhinolaryngological	53 (46.9)
Pulmonary	86 (76.1)
Cardiovascular	22 (19.5)
Gastrointestinal	5 (4.4)
Renal	68 (60.2)
Nervous systemic	42 (37.2)
Comorbidities at AAV diagnosis	
Diabetes mellitus	20 (17.7)
Hypertension	38 (33.6)
Dyslipidaemia	20 (17.7)
Laboratory results	
White blood cell count (/mm^3)	9,580.0 (7,003.0)
Neutrophil count (/mm^3)	7,165.0 (6,502.5)
Lymphocyte count (/mm^3)	1,290.0 (868.0)
Haemoglobin (g/dl)	10.8 (3.3)
Platelet count (×1,000/mm^3)	308.0 (170.0)
Fasting glucose (mg/dl)	101.0 (39.0)
Blood urea nitrogen (mg/dl)	19.4 (22.9)
Creatinine (mg/dl)	1.0 (1.8)
Total protein (g/dl)	6.4 (1.3)
Serum albumin (g/dl)	3.4 (1.2)
Acute phase reactants	
ESR (mm/h)	67.5 (77.0)
CRP (mg/l)	20.1 (92.52)
Interferon-gamma releasing assay (IGRA) results	
IGRA results [N, (%)]	
Positive	18 (15.9)
Negative	84 (74.3)
Indeterminate	11 (9.7)
Interferon-gamma levels	
Nil (IU/ml)	0.1 (0.1)
Tuberculosis antigen (IU/ml)	0.1 (0.1)
Mitogen (IU/ml)	10.0 (2.1)
Ex vivo interferon-gamma production (IU/ml)	9.8 (2.1)

Values are expressed as a median (interquartile range, IQR) or N (%). AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; ILD: interstitial lung disease; UIP: usual interstitial pneumonia.

the group with BVAS ≥18. Similarly, there was no significant difference in *ex vivo* IFN-gamma production between AAV patients with BVAS ≥18 and those with BVAS <18 (9.8 *vs*. 8.6 IU/ml, p=0.293) (Figure 1B).

AAV activity and IFN-gamma production in AAV patients without positive IGRA results. Among AAV patients with either indeterminate and negative or only negative IGRA results, a correlation between *ex vivo* production of IFN-gamma measured by IGRA and AAV activity assessed by BVAS was also evaluated; however, no significant correlations were found (Figure 2A and B).

Discussion

In this study, we investigated whether the levels of *ex vivo* production of IFN-gamma using IGRA were correlated with AAV activity assessed by BVAS and found that there was no statistically significant correlation between these two parameters despite the tendency. To date, there has been plenty of evidence supporting the role of IFN-gamma in cellular and humoral immunity in the pathogenesis of AAV (15-17). However, this study provided a paradoxical pattern of the correlation between *ex vivo* production of IFN-gamma and AAV activity in AAV patients. Based on these results, two hypotheses are proposed: first, the pattern of the inverse correlation is thought to be due to IFN-gamma producing T cell exhaustion, as shown in our previous study on systemic lupus erythematosus (SLE) (12). Several studies have supported this phenomenon by showing a marked decrease in T-cell responses to phytohemagglutinin A in patients with autoimmune diseases (18, 19). Second, the absence of statistical significance of this pattern indirectly indicated that the proportion of IFN-gamma in the pathogenesis of AAV is relatively smaller than that in SLE (8, 20).

Since extra-pulmonary tuberculosis accounts for approximately 20% (21), it is difficult to completely rule out latent tuberculosis using radiological methods, including chest computed tomography. In addition, it takes a long time to confirm the presence of latent tuberculosis in culture studies. In the same context, it can be argued that unidentified latent tuberculosis may affect *ex vivo* production of IFN-gamma to some extent in IGRA-positive AAV patients. Therefore, to exclude the effects of latent tuberculosis on the IGRA results, we divided the patients in two groups according to IGRA values: IGRA indeterminate and negative and IGRA negative only and evaluated the correlation between *ex vivo* production of IFN-gamma and AAV activity in these patients. However, there was no statistically significant correlation between the two variables. Therefore, it was concluded that *ex vivo* production of IFN-gamma by T cells in AAV patients might be diminished regardless of the IGRA results.

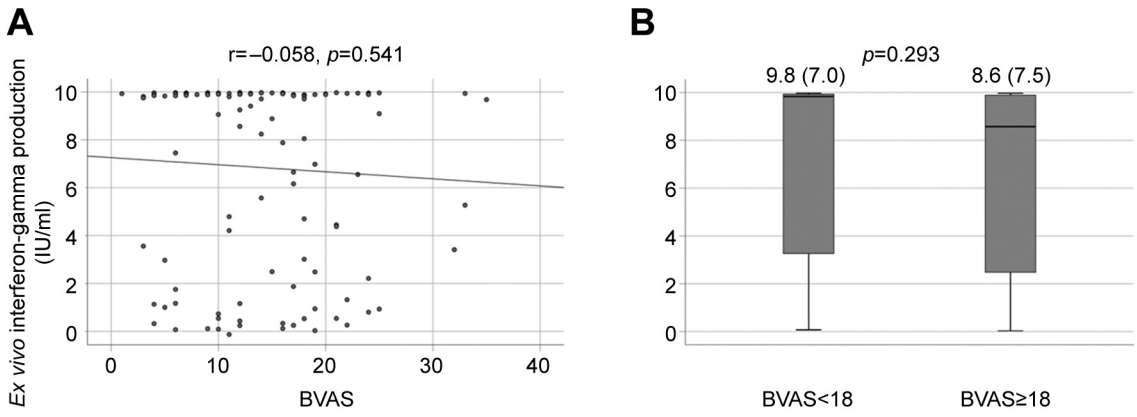

Figure 1. *Ex vivo interferon (IFN)-gamma production and Birmingham vasculitis activity score (BVAS). (A) There was no statistically significant correlation between ex vivo IFN-gamma production and BVAS in antineutrophil cytoplasmic antibody-associated vasculitis (AAV) patients; (B) there was no significant difference in ex vivo IFN-gamma production between AAV patients with BVAS ≥18 and those with BVAS <18.*

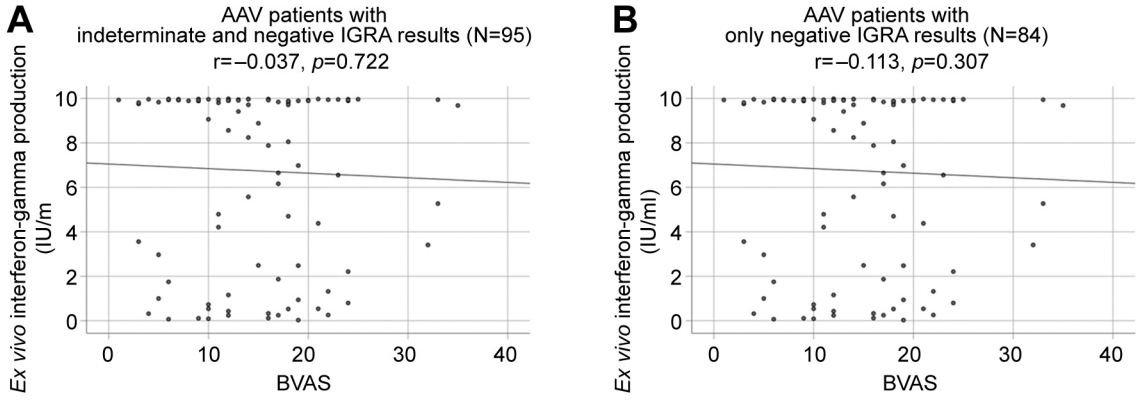

Figure 2. *Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) activity and interferon (IFN)-gamma production in AAV patients without positive IGRA tests. There were no statistically significant correlations between ex vivo IFN-gamma production and Birmingham vasculitis activity score in AAV patients with either indeterminate and negative IGRA results or only negative IGRA results.*

In actual clinical practice, when the administration of cyclophosphamide, rituximab, or a high dose of glucocorticoid is required in AAV patients, IGRA is performed first, and if positive, anti-tuberculosis prophylaxis therapy is currently recommended (22). If this study had demonstrated that *ex vivo* IFN-gamma production was significantly reduced in AAV patients with high disease activity, it would have been difficult to interpret the IGRA results. Taken together, these results constitute the first evidence supporting the IGRA results in AAV patients and showing they are relatively reliable, compared to the results obtained in patients with other autoimmune diseases.

The advantages of this study are that it included only AAV patients and investigated the levels of *ex vivo* production of IFN-gamma using IGRA for the first time. In addition, by revealing the absence of correlation between *ex vivo* production of IFN-gamma and AAV activity, this study provided valuable information on the reliability of the IGRA results for screening for latent tuberculosis in AAV patients before the administration of glucocorticoids and immunosuppressive drugs.

However, this study has several limitations. First, the number of patients was not sufficiently large to represent all AAV patients. In addition, this study did not include healthy controls or patients with other autoimmune systemic vasculitides; thus, we could not compare the IGRA results among them. However, given that the use of glucocorticoids and immunosuppressive drugs may have an influence on the IGRA results, and that Korea is one of the endemic areas of tuberculosis, we believe this study has clinical implications as a pilot study investigating *ex vivo* production of IFN-gamma using IGRA in AAV patients.

This study demonstrated, using IGRA, that AAV activity and *ex vivo* production of IFN-gamma in AAV patients are not

correlated. Therefore, this study provides information on the reliability of the IGRA results for screening for latent tuberculosis in AAV patients regardless of the activity of AAV.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, Sang-Won Lee; methodology, Jung Yoon Py; formal analysis, Jason Jungsik Song, Hyunsue Do and Sung Soo Ahn; analysis and data calculation, Hyunsue Do and Sung Soo Ahn; investigation, Jung Yoon Pyo; resources, Yong-Beom Park; data curation, Hyunsue Do; writing—original draft preparation, Hyunsue Do and Sung Soo Ahn; writing—review and editing, Sung Soo Ahn and Sang-Won Lee; visualization, Jason Jungsik Song; supervision, Sang-Won Lee; project administration, Sang-Won Lee; funding acquisition, Sung Soo Ahn and Sang-Won Lee.

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