Serum levels of the soluble haemoglobin scavenger receptor CD163 in MPO-ANCA-associated renal vasculitis

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Objectives: The contribution of infections to the mortality of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is important, and early and careful infection control is necessary. We investigated the usefulness of the serum-soluble haemoglobin scavenger receptor CD163 for detecting the presence of infectious complications regardless of disease activity.

Method: Soluble CD163 in serum obtained from 45 Japanese patients with myeloperoxidase (MPO)-AAV was measured by an enzyme-linked immunosorbent assay (ELISA). We evaluated 36 samples from active-vasculitis patients, 36 samples from inactive-vasculitis patients without infection, and 19 samples from inactive-vasculitis patients with infectious complications. Serum-soluble CD163 was also measured in 15 infectious patients without vasculitis and in 30 normal controls.

Results: The mean serum-soluble CD163 level was higher in the patients with infectious complications than in the active-vasculitis patients, inactive-vasculitis patients, and normal controls. There were significant positive correlations between serum-soluble CD163 levels and white blood cell (WBC) count, serum C-reactive protein (CRP) levels, and serum albumin levels, but only serum CRP levels were correlated with serum-soluble CD163 levels in a multiple regression analysis. On the receiver-operating characteristic (ROC) curve, serum-soluble CD163 levels had 80.6% sensitivity and 86.7% specificity for differentiating patients with infection from those without infection. Among the active-vasculitis patients, the mean serum-soluble CD163 level of the patients with alveolar haemorrhage was significantly lower than that of the patients with interstitial lung diseases and that of the patients without pulmonary lesions.

Conclusions: The serum-soluble CD163 level may be a useful marker for the detection of infectious complications in MPO-AAV patients.
by lipopolysaccharide, interferon (IFN)-γ, and tumour necrosis factor (TNF)-α and is up-regulated by interleukin (IL)-6 and IL-10 (9). Shedding of the extracellular domains of membrane-bound CD163 from the cell surface can be induced through TNF-α-converting enzyme (10) by phorbol esters (11) or lipopolysaccharide (12).

Increased serum levels of soluble CD163 have been observed in several infectious conditions, including sepsis/bacteraemia (13–15), meningitis (16, 17), pneumonia (17), and tuberculosis (18). Serum-soluble CD163 levels were also found to be elevated in autoimmune diseases such as rheumatoid arthritis (19–21), juvenile idiopathic arthritis (22), and systemic sclerosis (23). However, to our knowledge there has been no investigation of CD163 levels in patients with AAV. Therefore, to analyse the association between disease activity or infectious complications and CD163 in AAV, we investigated the serum levels of soluble CD163 in myeloperoxidase (MPO)-AAV patients.

Method

Patients

The cases of 45 Japanese patients with MPO-ANCA-associated microscopic polyangiitis (MPA) with renal involvement were examined. The diagnosis of MPA was based on the European Medicines Agency algorithm, and renal-limited vasculitis (RLV) was defined as the presence of only surrogate markers for renal vasculitis (24). Patients with GPA or eosinophilic granulomatosis with polyangiitis (EGPA) were excluded. The patients’ ANCA values were examined using an MPO-specific enzyme-linked immunosorbent assay (ELISA), and normal ranges were defined as values below 3.5 U/mL. Patients with a positive test result for proteinase-3-ANCA or anti-glomerular basement membrane antibody were excluded.

Of the 45 MPO-AAV patients, 36 provided serum samples before the initial treatment and 36 provided samples during remission (27 provided samples both before the initial treatment and during remission). Remission was defined as the absence of clinical disease activity based on the Birmingham Vasculitis Activity Score (BVAS). Nineteen samples obtained during remission with infectious complications were investigated. Twelve of the 19 patients with infectious complications had bacterial pneumonia, five had acute bronchitis, one had pulmonary tuberculosis, and the remaining patient had bacterial pleuritis.

As positive infectious controls, 10 patients with acute pyelonephritis and five patients with bacterial pneumonia were investigated. The diagnosis of acute pyelonephritis was based on characteristic clinical features including fever, costovertebral tenderness, leucocyturia, bacteria in urine sediment and urinary culture examination, elevated white blood cell (WBC) count, and elevated serum CRP level. The normal range of serum CRP is defined as a value below 0.3 mg/dL. The diagnosis of bacterial pneumonia was based on characteristic clinical features including fever, cough, sputum, elevated WBC count, serum CRP level, and chest X-ray findings.

As normal controls, 10 healthy volunteers and 20 patients with chronic kidney disease (CKD) were investigated. Ten of the 20 patients with CKD had nephropathy, two had autosomal-dominant polycystic kidney disease, two had diabetic nephropathy, and the other six had chronic glomerulonephritis. Patients with elevated levels of serum CRP were excluded from the group of normal controls.

The study protocol was accepted by the Ethics Committee of our institutes, and written informed consent was obtained from all patients or their immediate family members. This study also conformed to the provisions of the Declaration of Helsinki as revised in Edinburgh in 2000.

ELISA for serum-soluble CD163

Blood samples were collected in plasma separator tubes before the initial treatment, during remission, and at the time of complicating infection. Samples were separated at 1000g for 15 min and stored at −80°C for analysis. The samples were measured in duplicate using commercially available ELISA kits (Quantikine®, R&D Systems, Minneapolis, MN, USA). In brief, 100 µL/well of phosphate-buffered saline (PBS) with 1% bovine serum albumin (BSA) was added to 96-well microplates that had been coated with mouse monoclonal anti-human CD163 antibody. Then, 50 µL of a 10-fold-diluted sample was added to each well. Plates were incubated for 2 h at room temperature (RT) and then washed with PBS with 0.05% Tween-20, and horse radish peroxidase (HRP)-conjugated monoclonal anti-human CD163 antibody was added at 200 µL/well. The plates were incubated for 2 h at RT and then washed, and 100 µL of chromogen (tetramethylbenzidine) and 100 µL of hydrogen peroxide were added to each well. The plates were incubated for 30 min at RT, and 50 µL of 2N sulfuric acid solution was added to each well. The plates were immediately read on a microplate reader (Sunrise Remote®, Tecan Japan, Kanagawa, Japan) set at 450 nm for measurement and at 540 nm for wavelength correction. The inter- and intra-assay variations were < 10%.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (sd) and categorical variables are presented as numbers with percentages. Differences in categorical variables were checked using the χ² test with Yates’ continuity correction and Fisher’s exact test, and post-
hoc comparisons (Bonferroni correction) were performed to detect differences among three or more groups. An analysis of variance (ANOVA) was used to assess differences among patient groups, and post-hoc comparisons were made using the Bonferroni/Dunn test. A correlation analysis was performed using Spearman’s univariate correlation coefficient (r) to determine correlations between the serum levels of soluble CD163 and clinical parameters: age, BVAS, MPO-ANCA titre, WBC count, haemoglobin concentration, platelet count, and serum creatinine and CRP levels.

We performed a multiple linear regression analysis that included the covariates found to be significantly associated with the serum level of soluble CD163 in the correlation analysis. The data are expressed as standardized regression coefficients (β). A p-value < 0.05 was accepted as significant, but in the multiple comparisons, the p-value was divided by the number of comparisons being made. Comparative receiver-operating characteristic (ROC) curves for inflammatory variables of disease activity and diagnoses of infections were obtained. All statistical analyses were performed using PASW Statistics for Windows, version 18 (IBM Japan; formerly SPSS Japan Inc, Tokyo, Japan).

Results

Clinical parameters of subjects

There was no significant difference in age among the patients of the five groups: (i) the 36 active MPO-AAV patients, (ii) the 36 inactive-vasculitis patients without infection, (iii) the 19 inactive-vasculitis patients with infectious complications, (iv) the 15 infectious controls, and (v) the 30 normal controls, but the percentage of males was significantly lower in the infectious control group (Table 1). The MPO-ANCA titre was significantly higher in the patients with active vasculitis than in the other four groups (p < 0.0001), and MPO-ANCA was not detected in either control group.

Compared to the WBC counts of the normal controls, those of the patients with active vasculitis (p < 0.0001), inactive vasculitis without infectious complications (p = 0.0007), and inactive vasculitis with infectious complications (p < 0.0001) and those of the infectious controls (p < 0.0001) were significantly elevated. The WBC counts of the patients with active vasculitis without infectious complications were significantly lower than those of the patients with inactive vasculitis with infectious complications (p = 0.0002) and those of the infectious controls (p < 0.0001).

Compared to the serum CRP levels among the normal controls, those of the patients with active vasculitis (p < 0.0001) or inactive vasculitis with infectious complications (p < 0.0001) and those of the infectious controls (p < 0.0001) were significantly elevated. The mean serum CRP level of the inactive-vasculitis patients without infection was significantly lower than that of the active-vasculitis patients (p < 0.0001), the inactive-vasculitis patients with infectious complications (p < 0.0001), and the infectious controls (p < 0.0001). The mean serum creatinine level was also significantly

Table 1. Characteristics of the five patient groups.

|                     | Active vasculitis (n = 36) | Inactive vasculitis (n = 36) | Inactive vasculitis with infections (n = 19) | Infectious controls (n = 15) | Normal controls (n = 30) |
|---------------------|----------------------------|-----------------------------|---------------------------------------------|----------------------------|--------------------------|
| Age (years)         | 70.8 ± 13.7                | 69.2 ± 13.4                 | 70.5 ± 9.5                                  | 70.3 ± 18.4                | 68.9 ± 13.1              |
| Male gender         | 20 (56)                    | 19 (53)                     | 10 (53)                                     | 21 (13)                    | 15 (50)                  |
| Classification      |                            |                             |                                             |                            |                          |
| MPA                 | 26 (72)                    | 23 (64)                     | 14 (74)                                     |                            |                          |
| RLV                 | 10 (28)                    | 13 (36)                     | 5 (26)                                      |                            |                          |
| Pulmonary features* |                            |                             |                                             |                            |                          |
| DAH                 | 8 (22)                     | 6 (17)                      | 3 (16)                                      |                            |                          |
| IPD                 | 17 (47)                    | 16 (44)                     | 10 (52)                                     |                            |                          |
| None                | 11 (31)                    | 14 (39)                     | 6 (32)                                      |                            |                          |
| BVAS                | 21.6 ± 5.2                 | 0 ± 0                       | 0 ± 0                                       | 0 ± 0                      |                          |
| MPO-ANCA (U/mL)     | 241.4 ± 181.51 ± ##‡       | 19.0 ± 34.7                 | 48.3 ± 112.9                                | 13 ± 0                     | 13 ± 0                   |
| White blood cells (×10⁶/mm³) | 9735 ± 35151 | 8657 ± 3139a | 12 413 ± 3039 ± † | 13 080 ± 5156 ± | 5800 ± 1503 |
| Haemoglobin (g/dL)  | 9.3 ± 2.1                  | 11.7 ± 2.0                  | 10.8 ± 2.8                                  | 12.4 ± 1.8                 | 12.3 ± 2.0               |
| Platelets (×10⁹/mm³) | 27.5 ± 12.5                | 21.9 ± 4.6                  | 20.8 ± 10.8                                 | 19.9 ± 7.3                 | 19.8 ± 6.0               |
| Serum albumin (g/dL) | 3.01 ± 0.62 ± †             | 3.71 ± 0.38t                | 3.21 ± 0.781 ± †                            | 3.75 ± 0.44                | 4.16 ± 0.33              |
| Serum creatinine (mg/dL) | 4.52 ± 3.43t             | 3.45 ± 4.30                 | 2.58 ± 2.27                                | 1.26 ± 0.73                | 1.60 ± 1.15              |
| Serum CRP (mg/dL)   | 8.15 ± 6.801 ± †           | 0.19 ± 0.15                 | 8.78 ± 5.401 ± †                           | 12.40 ± 7.461 ± †          | 0.08 ± 0.12              |

ANCA, Anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CPA, chance proteinuria and haematuria; CRP, C-reactive protein; DAH, diffuse alveolar haemorrhage; IPD, interstitial pulmonary disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; RLV, renal-limited vasculitis.

Variables are expressed as mean ± standard deviation or number (percentage of the total).

* These feature were observed at the onset of vasculitis.
† p < 0.005 vs. normal controls; † p < 0.005 vs. infectious controls; § p < 0.005 vs. inactive-vasculitis with infection; ¶ p < 0.005 vs. inactive-vasculitis; †† p < 0.005 vs. active-vasculitis.

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higher in the active-vasculitis patients than in both infectious and normal control groups (p = 0.0006 and p = 0.0002, respectively).

Serum levels of soluble CD163

The serum levels of soluble CD163 were significantly higher in the inactive-vasculitis patients with infectious complications compared to the active-vasculitis patients, the inactive-vasculitis patients, and the normal controls (p < 0.0001, respectively, Figure 1). These levels were significantly higher in the infectious controls compared to the active-vasculitis patients, the inactive-vasculitis patients, and the normal controls (p = 0.0003, p < 0.0001, and p < 0.0001, respectively).

There were no significant correlations between the serum levels of soluble CD163 and age, BVAS, MPO-ANCA titre, haemoglobin concentration, platelet count, or serum creatinine level. There were significant positive correlations between the serum levels of soluble CD163 and the WBC count (r = 0.440, p < 0.0001) and the serum CRP level (r = 0.420, p < 0.0001), and there were significant negative correlations between the serum levels of soluble CD163 and albumin (r = −0.283, p = 0.0013). In the multiple regression analysis including the above three variables, there were significant positive correlations between the serum levels of soluble CD163 and the serum CRP levels (β = 0.304, p = 0.0031).

ROC curve analysis

The comparative ROC curves for three measures (WBC count, serum CRP level, and serum level of soluble CD163) of disease activity and the diagnosis of infection are shown in Figure 2. The optimum cut-off levels for the diagnosis of infection were identified from the ROC curves for WBC count (> 10 150/mm³), serum CRP level (> 1.56 mg/dL), and serum level of soluble CD163 (> 762.8 ng/mL). The area under the curve (AUC) for the serum level of soluble CD163 was 0.904, which is higher than those of the WBC count (0.829) and the serum CRP level (0.854). On the ROC curve, the serum level of soluble CD163 had 80.6% sensitivity and 86.7% specificity for differentiating patients with infection from those without infection. Although the sensitivity of the serum-soluble CD163 level was less than that of the serum CRP level (93.5%), the specificity of these parameters was superior to that of the serum CRP level (72.4%).

Relationship between the serum level of soluble CD163 and pulmonary involvement

The serum levels of soluble CD163 were significantly lower in the active-vasculitis patients with MPA compared to those with RLV (p = 0.0007).

Because all of the MPA patients had pulmonary involvement, we divided the active-vasculitis patients with MPA into four groups: (i) active MPO-AAV patients with alveolar haemorrhage, (ii) active-vasculitis patients with interstitial lung disease, (iii) active-vasculitis patients with pulmonary granuloma, and (iv) active-vasculitis patients without pulmonary involvement. Eight active MPO-AAV patients had alveolar haemorrhage and 17 had interstitial lung diseases, but there were no active-vasculitis patients with pulmonary granuloma.

The serum levels of soluble CD163 were significantly lower in the active-AAV patients with alveolar haemorrhage compared to those with interstitial pulmonary disease and those without pulmonary involvement (p < 0.0001 and p < 0.0001, respectively, Figure 3 and Supplementary Data).

Discussion

Elevated levels of serum-soluble CD163 have been demonstrated in several autoimmune diseases (19–23) but the results of the present analysis show that those levels are not associated with disease activity in AAV. However, we did find that the serum level of soluble CD163 was elevated in infectious patients with or without AAV, similar to previous investigations (13–16). On the comparative ROC curves, the specificity and the sensitivity of the serum-soluble CD163 levels for the diagnosis of infectious diseases were far superior to those of the WBC count, and the specificity was far superior to that of serum CRP levels. Therefore, the serum level of soluble CD163 in AAV patients may be used to detect infectious complications compared with vasculitis.

We previously demonstrated the efficacy of serum-soluble TREM-1 to detect the presence of infectious complications in AAV patients (4). The level of serum-soluble
TREM-1 depends on the patient’s renal function but the serum level of soluble CD163 is not related to renal function. Considering that rapidly progressive glomerulonephritis (RPGN) is often observed in AAV patients, serum-soluble CD163 may be a more suitable biomarker of infectious complications than serum-soluble TREM-1. Moreover, in the present study the AUC of the serum-soluble CD163 levels for the diagnosis of infectious diseases was 0.904, which is superior to that of the serum ratio of soluble TREM-1 to creatinine (0.882).

We observed that the sensitivity of the serum-soluble CD163 level for the diagnosis of infectious diseases was far inferior to that of the serum CRP level. Moreover, the serum-soluble CD163 levels in every infectious group were not significantly elevated compared to those of the subjects without infection (Supplementary Data), so it may be difficult to differentiate AAV patients with infection from those without infection by only the measurement of serum-soluble CD163 levels. To differentiate patients with infection from those without infection, various biomarkers measured in combination may be best, because all of the existing markers have disadvantages.

In the present study, the standard deviation of the serum-soluble CD163 levels of the active-vasculitis patients was the widest among the five groups. Some of the active-vasculitis patients who had elevated levels of serum-soluble CD163 may still have been complicated with infectious diseases after their treatment with antibiotics. By contrast, the serum levels of soluble CD163 of the MPO-AAV patients with alveolar haemorrhage were significantly decreased. The mechanisms of decreased serum-soluble CD163 levels in haemorrhagic complications have not been identified. Further experimental studies are needed to identify the mechanisms of the decreased serum-soluble CD163 levels in haemorrhagic complications.

Our study has several limitations. First, the study population was limited to Japanese patients with MPO-ANCA-associated renal vasculitis because of the low incidence of PR3-AAV (or GPA) in Japan. Further studies are necessary to compare patients with PR3-ANCA-associated vasculitis or non-renal vasculitis. Moreover, a potential genetic bias may prevent the applicability of our results to non-Japanese populations.
In addition, this study was a retrospective cross-sectional analysis; a larger prospective longitudinal study would provide more definitive results.

In summary, the serum levels of soluble CD163 were elevated in AAV patients with infectious complications, and the combined measurements of various biomarkers including serum-soluble CD163 may be useful for the detection of infectious complications in MPO-AAV patients.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table 1. Serum soluble CD163 levels correlation among 11 groups.

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