CIRCULATING CD24hiCD38hi REGULATORY B CELLS
INFLUENCE TH17 CELL RESPONSES IN PATIENTS
WITH ANCA-ASSOCIATED VASCULITIDES

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Background: CD24hiCD38hi regulatory B cells (Bregs) exhibit suppressive function and modulate pathogenic T cell responses. Persistent expansion of pathogenic IL-17-producing T cells (Th17) has been demonstrated in patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV). In addition, a reduction in numbers of CD24hiCD38hi Bregs was described in active AAV patients whereas no difference was found in patients in remission compared to healthy controls (HCs).

Objectives: To investigate whether there is a direct relationship between increased proportions of Th17 cells and diminished proportions Bregs in AAV patients.

Methods: Frequencies of both Bregs and Th17 cells were determined by FACS in blood samples from 44 AAV patients in remission. None of the AAV patients received immunosuppressive treatment. Bregs were defined within the CD19 population as CD24hiCD38hi cells, and Th17 cells were defined within the CD3+CD4+CD45RO+ population as CD24 hiCD38 hi cells, and Th17 cells were defined within the CD3+CD4+CD45RO+ population by their specific chemokine receptor expression as CXCR3-CCR4+CCR6+ cells. In addition, CD3+CD4+ Th cells were sorted from 4 AAV patients and 3 HCs and co-cultured with either Breg-depleted B cells or total B cells. Culture cells were stimulated with SEB and Cpg-ODN and frequencies of both IL-17 (Th17) and IFNγ (Th1) T cells were determined at baseline and day 5 upon restimulation with PMA and Cd45+ ionophore.

Results: The frequency of circulating Bregs in AAV-patients correlated negatively with circulating Th17 cells (r=-0.390; p<0.009), whereas no such correlation was observed with other B cell subtypes. The co-culture experiments revealed that the frequency of IFNγ Th cells was unaffected when Bregs were depleted in both HCs and AAV patients (undepleted samples median: 10.6%; range: 5.5%–19.7% vs Breg-depleted samples median: 11%; range: 4.9%–19.2%). Remarkably, a significant increase in the frequency of IL-17 Th cells was detected in Breg-depleted samples (median: 1.6%; range: 1%–3.8%) compared to undepleted samples in both HCs and patients (p=0.03; undepleted samples median: 1.2%; range: 0.9%–2.9%). Moreover, the IFNγ:IL-17 Th cell ratio was not different between undepleted (median: 13.8; range: 5.1–39.3) and Breg-depleted samples at baseline (median: 11; range: 7.3–30), whereas a significant decrease was found in the Breg-depleted samples (median: 5.6; range: 3.3–9.1) after 5 days of culture (p<0.001; undepleted median: 6.3; range: 4.2–10.6) indicating a change in the Th1:Th17 ratio.

Conclusions: CD24 hiCD38hi Bregs modulate Th17 responses in AAV patients. Future treatment of AAV could aim at expanding CD24 hiCD38 hi Bregs to suppress pathogenic Th17 cells.

Disclosure of Interest: None declared


THE UTILITY OF SERUM ANGIOPOIETIN-1 AND ANGIOPOIETIN-2 IN PATIENTS WITH ANTI-NEUTROPHIL CYTOLPLASMIC AUTOANTIBODY-ASSOCIATED VASCULITIS

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Background: Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2) are antagonistic ligands which bind with similar affinity to the extracellular domain of the tyrosine kinase with Ig-like and epidermal growth factor-like domains 2 (Tie-2) receptor, which is almost exclusively expressed by endothelial cells. Ang-1/Tie-2 signalling maintains vessel integrity, inhibits vascular leakage, suppresses inflammatory gene expression and prevents recruitment and transmigration of leucocytes. In contrast, binding of Ang-2 disrupts protective Ang-1/Tie-2 signalling and facilitates endothelial inflammation. Recently, serum Ang-2 levels have been reported to be elevated in autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and anti-neutrophil cytoplasmatic autoantibody-associated vasculitis (AAV).

Objectives: To examine the serum Ang-1 and Ang-2 levels in patients with AAV, and investigate the utility as biomarkers.

Methods: Seventy-one patients who had been diagnosed as AAV and referred to Niigata University Medical and Dental Hospital between 2009 and 2017, were participated in this study. Serum Ang-1 and Ang-2 levels were measured by enzyme-linked immunosorbent assay, before the initiation of remission-induction therapy. Laboratory findings, disease activity using Birmingham vasculitis activity score (BVAS) at the time of diagnosis, and patients’ kidney and overall prognosis at August 2017, were corrected from patients’ clinical records. The correlations between these findings and serum Ang-1, Ang-2 levels, and Ang-1/Ang-2 ratio were analysed by Pearson correlation coefficient and stepwise multiple regression analysis. A value of p<0.05 was taken to indicate statistical significance.

Results: In Pearson correlation coefficient analysis, serum Ang-1 was negatively correlated with serum creatinine (Cr) (r=-0.3490, p=0.0151), uric acid/creatinine ratio (UP/Cr) (r=-0.3147, p=0.0312), and positively correlated with estimated glomerular filtration rate (eGFR) (r=0.4091, p=0.0039). Serum Ang-2 was positively correlated with BVAS (r=0.3024, p=0.003), serum Cr (r=0.3778, p=0.0081), and the initiation of hemodialysis therapy (r=0.4196, p=0.0151), and negatively correlated with eGFR (r=-0.2999, p=0.0383). The Ang-1/Ang-2 ratio was positively correlated with BVAS (r=0.3527, p=0.0139), serum Cr (r=0.7419, p=0.0001), UP/Cre (r=0.4799, p=0.0006), and the initiation of hemodialysis therapy (r=0.6151, p=0.0001), and negatively correlated with eGFR (r=-0.4758, p=0.0056). In stepwise multiple regression analysis, eGFR was selected as a positive independent variable for serum Ang-1 levels (beta=0.3769, p=0.0014) and Ang-1/Ang-2 ratio (beta=0.4060, p=0.0005), whereas the initiation of hemodialysis therapy was selected as a positive independent variable (beta=0.5850, p=0.0001), and UP/Cre (beta=0.5780, p=0.0001) and eGFR (beta=-0.4311, p=0.0003) were selected as negative independent variables for serum Ang-2 levels (beta=-0.4620, p=0.0007).

Conclusions: These findings showed the protective effect of kidney functions for Ang-1 and the utility of Ang-2 as a predictive factor for kidney prognosis.

REFERENCES:

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