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Circulating IgG4 antibody secreting cells is a better biomarker of disease activity compared to serum IgG4 level in patients with IgG4-related disease**Arezou Khosroshahi, Alessia Corrado, Shuya Kyu, Xiaoqian Wang, Ignacio Sanz and F Eun-Hyung Lee**
Emory University Hospital, USA

Background & Purpose: IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition with a consistent set of pathological features that affects multiple organ systems. Patients with IgG4-RD typically present with mass lesions in different organs. Clinical and radiologic findings usually resemble malignancy, infection or other autoimmune diseases making the diagnosis challenging. Up to now, the best marker of the disease is elevated serum IgG4 concentrations, however, many different studies find that this analyte is not a reliable disease biomarker, at least as measured by current immunoassays. We hypothesized that reliance on elevated serum IgG4 concentration fails to identify a significant fraction of patients, at least partly due to assay limitations. Here, we describe the direct measurement of IgG4 production by circulating Antibody Secreting Cells (ASC) as a more reliable biomarker for diagnosis and disease activity monitoring in patients with IgG4-RD.

Method: This study compared serum IgG4 levels measured by nephelometry assay with frequency of IgG4 ASC in blood measured with IgG4 Elispot (Enzyme-linked immunospot) assay. We enrolled 34 IgG4-RD patients with various degrees of disease activity, 6 patients with diseases mimicking IgG4-RD and 7 healthy controls. Using the IgG4-RD Responder Index (RI), where an $RI \geq 3$ is regarded as active disease, we had 24 patients with active disease. We used multivariate analysis and Pearson-correlation for statistical comparison.

Result: Serum IgG4 concentration was elevated in 10 IgG4-RD patients (29%) while increased IgG4/IgG percentages in Elispots ($>5\%$ IgG4/IgG) occurred in 27 patients (79%). All IgG4-RD patients who had serum elevation showed IgG4/IgG $>5\%$ in the Elispot assay. Among patients who had normal serum IgG4 by nephelometry but elevated number of IgG4 on the Elispot 13 out of 15 had active IgG4-RD with responder index (IgG4-RD RI) score of ≥ 3 . Of the patients with active IgG4-RD ($RI \geq 3$), 18 of 26 (77%) had IgG4/IgG ASC percentages $>5\%$ compared with only 6 out of 26 (23%) with elevated serum IgG4 ($r: 0.36$ $p: 0.029$). Furthermore, among the control group, one subject had elevated serum IgG4 at 176 mg/dl (normal=0-89 mg/dl) but normal Elispot IgG4/IgG percentages 1.2% ($<5\%$) showing improved specificity.

Conclusion: Circulating IgG4/IgG ASC percentages $>5\%$ is a more sensitive and reliable marker for disease activity in patients with IgG4-RD both for diagnosis and disease activity monitoring. This method overcomes spurious low serum IgG4 levels due to the prozone phenomenon, cell binding and another unknown phenomenon. This preliminary study shows that IgG4 ASC Elispots are sensitive markers for IgG4-RD.

akhosroshahi@emory.edu