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203. LYMPHOCYTES, LYMPHOCYTE ACTIVATION, AND IMMUNODEFICIENCY, INCLUDING HIV AND OTHER INFECTIONS: POSTER III | DECEMBER 07, 2017

Quantification of Plasma Proteins from Idiopathic Multicentric Castleman Disease Flares and Remissions Reveals 'Chemokine Storm' and Separates Clinical Subtypes

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Blood blood **(2017) 130 (Suppl_1) : 3592.**

http://doi.org/10.1182/blood.V130.Suppl_1.3592.3592

Abstract

Introduction: Human Herpesvirus-8(HHV-8)-negative/idiopathic multicentric Castleman disease (iMCD) is a poorly understood disease involving polyclonal lymphoproliferation, constitutional symptoms, and life-threatening multi-organ failure. Some patients experience thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly (TAFRO Syndrome) while others (non-TAFRO) experience thrombocytosis and hypergammaglobulinemia. Though the etiology is unknown, iMCD symptoms and disease progression are believed to be driven by a cytokine storm, often including interleukin-6 (IL-6). Anti-IL-6 therapy with siltuximab was approved by the FDA to treat iMCD based on superior efficacy compared to placebo in a randomized trial. However, approximately one-half of iMCD patients do not respond to anti-IL-6 therapy. Few rational treatment options exist for anti-IL-6 non-responders, because alternative driver cytokines and signaling pathways are not known. Furthermore, no positive diagnostic biomarkers exist for iMCD. We systematically characterized proteomic changes that occur in iMCD patients between flare and remission to identify key cytokines, signaling pathways, and cell types that may be involved in pathogenesis.

Methods: Using Somalogic's modified aptamer-based proteomics platform, SOMAScan, we quantified 1,129 plasma proteins from six iMCD patients at the University of Arkansas for Medical Sciences during flare and remission. Two cases were confirmed to have TAFRO syndrome, and four cases did not have TAFRO syndrome. Proteomic data for two sets of healthy controls were obtained post-hoc and merged with the iMCD proteomic data along common calibrated proteins. Data analysis was performed using R 3.3.3.

Results: Principal component analysis (PCA) revealed a distinction between iMCD samples-in flare and remission-and healthy control samples. Reactome pathway analyses identified cytokine signaling, chemokine signaling, and the complement cascade as the most enriched pathways compared to the background proteins assayed. Chemokines represented the greatest proportion of two-fold up-regulated cytokines in flare compared to interleukins and other cytokines. The chemokine, B Lymphocyte Chemoattractant (BLC)/CXCL13, was the most significantly upregulated cytokine across all patients. IL-6 was surprisingly not among the most upregulated cytokines. Five of six patients had less than two-fold up-regulation and the only patient with greater than two-fold up-regulation did not improve with anti-IL-6 receptor monotherapy. However, three of the other four patients treated with anti-IL-6 or anti-IL-6 receptor monotherapy experienced responses despite small changes in IL-6 levels between flare and remission. We observed a distinct proteomic profile between the TAFRO and non-TAFRO patients according to PCA, correlation analyses, and hierarchical clustering. The two TAFRO patients also both failed to respond to anti-IL-6 monotherapy. A large proportion of proteins significantly up- or down-regulated in non-TAFRO patients were conversely up- or down-regulated in TAFRO patients.

Discussion: This study provides the first unbiased quantification of circulating proteins in iMCD patients during flare and remission. PCA of these data suggest that the proteomic profile of iMCD patients differs from that of healthy individuals even during remission. Our results support the field's assertion that iMCD involves a cytokine storm, but increased IL-6 was not uniformly present. The response of three patients to anti-IL-6 treatment suggests that IL-6 plays a critical role in these patients despite subtle changes in IL-6 levels. The increased proportion of up-regulated chemokines relative to other cytokines suggests that iMCD involves a chemokine storm. CXCL13 plays an essential role in honing B cells to germinal centers, which are uniformly dysmorphic in iMCD with either too few (atrophic) or too many B cells (hyperplastic). Lymph node stromal cells are known to produce three of the most up-regulated chemokines (CXCL13, CCL19 and CCL21), suggesting that they may play a role in pathogenesis. The distinct proteomic profiles between TAFRO (both anti-IL-6 non-responders) and non-TAFRO (responders) cases suggest that differing mechanisms may be involved. Larger studies are needed to confirm these findings and investigate chemokines in iMCD pathogenesis.

Disclosures

Fajgenbaum: *Janssen Pharmaceuticals:* Research Funding.

Author notes

*Asterisk with author names denotes non-ASH members.