Novel Modular Analysis of Microarray Data to Follow Response to IL-1 Blockade in SoJIA Patients

Systemic onset JIA (SoJIA) is unique in terms of its clinical manifestations, prognosis, and response to therapy. Previous studies have shown the importance of IL-1b in the pathogenesis of SoJIA [Pascual V et al. *J Exp Med* 2005] and the beneficial effects of anti-IL1 in controlling the clinical manifestations of the disease [Allantaz F. *J Exp Med* 2007; Verbsky JW and White AJ. *J Rheumatol* 2004].

Florence Allantaz, PhD, Baylor Institute for Immunology Research, Dallas, TX, presented the results of a multicenter randomized double-blind trial (NCT00339157) conducted in patients with SoJIA (n=24). The objectives of the study were to investigate immunological mechanisms underlying the disease and assess the effect of anakinra at a transcriptional level using patient blood transcriptional profiles. During the double-blind phase of the study (Month 1) patients received either anakinra (2 mg/kg/day; maximum 100 mg) or placebo; patients received anakinra for the remaining 5 months.

Blood samples were collected at enrollment and at Months 1 and 6. Whole blood RNA was hybridized to Illumina Human 6-v2 chips. A module-based data mining strategy, which focused the analysis of microarray data on stable sets of transcripts selected on the basis of their clustering pattern across diseases, was used.

At Day 1, modular analysis showed significantly increased expression of genes related to cells of the myeloid lineage (ie, monocytes and neutrophils, inflammation, red blood cells, and coagulation-related genes), reflecting a strong activation of the innate immune response. Dr. Allantaz and colleagues also observed a consistent down-regulation of genes regulating adaptive immunity, including genes associated with B cell, T cell and cytotoxic cell function of genes involved in immunosuppression were also downregulated. After 6 months of treatment with anakinra, the dysregulation of those modules rapidly disappeared in 13/19 patients, indicating that anakinra is an effective treatment for SoJIA.

This analysis also showed that IFN-regulated genes were induced with anakinra treatment. One month of treatment was sufficient to induce significant changes in modular expression and allow the investigators to distinguish patients treated with anakinra from patients treated with placebo. Modular analyses at Months 1 and 6 also showed clear differences between responders and nonresponders.

Dr. Allantaz stated, "Using a modular based approach we were able to identify a set of gene pathways dysregulated in SoJIA whose expression dramatically changed upon anakinra treatment in a group of patients."

The safety and efficacy results of this trial were also presented during the EULAR 2008 Annual Meeting [Abstract OP-0061] and have recently been published [Quartier P et al. *Ann Rheum Dis* 2008;67(Suppl II):68].

Highlights from the
European League Against Rheumatism 2008 Annual Meeting