Novel Approach to Inhibit Asthma-Mediated Lung Inflammation Using Anti-CD147 Intervention


PURPOSE OF THE STUDY. Extracellular cyclophilins are known to promote chemotaxis of various leukocyte subsets through interaction with the cell surface signaling receptor CD147. Increased levels of extracellular cyclophilins have been reported in various inflammatory diseases. This study investigated whether extracellular cyclophilin-CD147 interaction plays a role in the recruitment of leukocytes in asthmatic lung inflammation.

METHODS. A mouse model of allergic asthma was created by intraperitoneal ovalbumin injection into newborn mice, followed by intranasal ovalbumin challenge on days 7 to 10. For in vivo inhibition studies, anti-CD147 was administered intraperitoneally on days 6 to 11. Bronchial hyperreactivity was assessed on day 12. After sacrifice on day 12, the following were examined: histology on bronchoalveolar lavage (BAL) and lung biopsy, cytokine levels after restimulation of pulmonary lymphocytes with ovalbumin antigen, cyclophilin (Cyp) A and CypB levels in BAL fluid by Western blot analysis, chemotaxis of eosinophils and CD4+ splenocytes to CypA and CypB, and CD147 expression levels on CD4+ T cells by fluorescence-activated cell sorter analysis.

RESULTS. The mouse model of asthma-mediated lung inflammation was confirmed by the findings of elevated eosinophils and lymphocytes in the BAL of ovalbumin mice, elevated interleukin 5 (IL-5) and IL-13 in lung cell supernatant from ovalbumin mice cells restimulated with antigen, and airway hyperresponsiveness to methacholine in ovalbumin mice. The main study findings were: (1) extracellular CypA and CypB levels were significantly increased in the airways of asthmatic mice; (2) CD147 was expressed by mouse eosinophils and CD4+ T cells and upregulated in activated CD4+ T cells; (3) CypA and CypB induced CD147-dependent chemotaxis of activated mouse CD4+ T cells but not eosinophils; (4) in vivo anti-CD147 monoclonal antibody (mAb) treatment resulted in a significant (up to 50%) decrease in the numbers of eosinophils and CD4+ T cells in lung tissues of ovalbumin mice, as well as a reduction in antigen-specific Th2 cytokine (IL-5 and IL-13) secretion; and (5) anti-CD147 mAb treatment reduced airway epithelial mucin production and bronchial hyperreactivity.

CONCLUSIONS. This study suggests that extracellular cyclophilins, through interaction with CD147, play a role in asthma-mediated lung inflammation and that anti-CD147 intervention significantly reduces several parameters of this inflammation.

Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1β Inhibition


PURPOSE OF THE STUDY. Neonatal-onset multisystem inflammatory disease (NOMID) is a chronic inflammatory disease that develops in infancy and is characterized by an urticarial rash, arthropathy, and central nervous system disease, including aseptic meningitis, cerebral atrophy, mental retardation, seizures, and vision and hearing loss. Approximately 60% of patients have a mutation in the cold-induced autoinflammatory syndrome 1 (*CIAS1*) gene, which is involved in the interleukin 1β (IL-1β) pathway. This study evaluated the effect of anakinra (Kineret, Amgen), an IL-1 receptor antagonist, on the various clinical and laboratory aspects of NOMID.

STUDY POPULATION. A cohort of 18 patients aged 4 to 32 years with clinical NOMID (67% with mutations in *CIAS1*) who had active disease despite treatment with other antiinflammatory agents.

METHODS. Patients were given a daily subcutaneous dose of anakinra. The drug was withdrawn from 11 patients at 3 months with the development of a clinical flare. Thereafter, all patients were continued on daily treatments up to 24 months. Clinical and laboratory assessments were made at 1, 3, and 6 months during therapy with anakinra. Primary end points included changes in a disease-specific daily diary score and changes in the serum levels of acute-phase reactants.

RESULTS. All patients had an immediate response to anakinra with resolution of rash and conjunctivitis. There
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DOI: 10.1542/peds.2007-0846JJJJ

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