RITUXIMAB DEPLETES B-LYMPHOCYTES IN PULMONARY ALVEOLAR PROTEINOSIS

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Background: Pulmonary Alveolar Proteinosis (PAP) is an autoimmune disorder characterized by autoantibodies to GM-CSF. Rituximab, a chimeric murine-human monoclonal antibody, directed against the B lymphocyte specific antigen CD20, has shown promise in a number of autoimmune disorders. We hypothesized that Rituximab would deplete B-lymphocytes in PAP and thus improve clinical condition.

Methods: As part of an open label proof-of-concept Phase II clinical trial of 10 patients, to date, 7 PAP patients received two infusions (1mg/ml) of Rituximab, fifteen days apart. Peripheral blood samples were collected from patients both pre- and post-Rituximab infusion. Lymphocyte activation was determined by measurement of ATP using CD4 magnetic bead assays (Cylex). Peripheral blood mononuclear cells (PBMC) were also isolated from both PAP patients and healthy controls and analyzed by flow cytometry. Oxygenation of PAP patients was measured by PaO2.

Results: B-lymphocytes decreased by 15±2 % (n=7) by fifteen days post therapy and persisted for 6 months. T-lymphocyte activity increased by 55% following administration of Rituximab, persisting three months post therapy (n=5), as compared to <1% increase in activity of T-lymphocytes from healthy controls (n=4). Oxygenation was also determined to be improved by 14±5 mmHg in 4/5 patients.

Conclusions: Administration of Rituximab to PAP patients effectively depleted B- lymphocytes and enhanced T-lymphocyte activity, suggesting that in PAP, Rituximab affects both humoral and cellular immune systems. Rituximab also improved clinical symptoms, indicating that therapy directed at the autoimmune pathogenesis of PAP represents an effective and beneficial approach.