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Mechanism of action and clinical efficacy of mTOR blockade in lupus

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Systemic lupus erythematosus (SLE) is an autoimmune disease affecting 1.5 million Americans with ~10% mortality over 5 years. Our recent studies unveiled a significant involvement of the mechanistic target of rapamycin (mTOR) in abnormal T-cell activation and lineage specification and autoantibody production in SLE. In accordance with a critical role for mTOR in pathogenesis, rapamycin reduced disease activity in a recently completed clinical trial. Metabolome triggers of mTOR activation and clinical responsiveness in SLE: systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology with mortality still approaching 10% over 5 years. Although prevalence estimates vary, 1.5 million people are thought to have SLE in the United States. There is unmet medical need, as current treatments are only partially effective and have significant side effects. Our central hypothesis has been formulated on the basis of growing evidence for significant involvement of mTOR activation in abnormal T-cell activation and lineage specification and its impact on B-cell activation and production of antinuclear autoantibodies (ANA). The rationale for this study is supported by existing data in the literature providing evidence that 1) mTOR activity is increased in T cells of patients and mice with SLE; 2) mTOR controls T cells lineage specification during development and its skewing in SLE; 3) administration of rapamycin improves the clinical outcome of lupus in mice and patients; 4) rapamycin enhances renal allograft survival in patients with antiphospholipid antibodies, which represent a diagnostic criterion and a source of co-morbidity is SLE; and 5) mTOR blockade with rapamycin is known to be safe and increase overall lifespan, at least in mice. Therefore, we initiated a prospective study of rapamycin for the treatment of SLE (ClinicalTrials.gov Identifier: NCT00779194). In accordance with a critical role for mTOR in lupus pathogenesis, the blockade of mTOR reduced disease activity in 126±18 days as evidenced by well-tolerated rapamycin plasma levels of 8.7±1.2 ng/ml, which was within the targeted therapeutic range of 6-15 ng/ml. SLEDAI disease activity scores were reduced to 5.7±1.0 from 11.8±1.1 at baseline (p=0.0028). Among the patients who completed the 1 year intervention thus far, an SLE responder index of 64.3% was achieved. Rapamycin inhibited the pro-inflammatory expansion and IL-4 production of CD4-CD8- double-negative (DN) T cells, which have been found to stimulate anti-DNA production by B cells. Given that the blockade of mTORC1 abrogates disease activity in mice and patients with SLE, it is important to further establish the efficacy of rapamycin in a randomized double-blind placebo-controlled clinical trial.

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