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1: J Am Soc Nephrol. 2008 Mar;19(3):631-8. Epub 2008 Jan 16.

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Sirolimus reduces polycystic liver volume in ADPKD patients.

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The immunosuppressive agent sirolimus exerts an antiproliferative effect by inhibiting mammalian target of rapamycin (mTOR). Because excessive proliferation of the biliary epithelium is a prominent feature of the polycystic liver that accompanies autosomal dominant polycystic kidney disease (ADPKD), we hypothesized that sirolimus may benefit patients with this disorder. We retrospectively measured the volumes of polycystic livers and kidneys in ADPKD patients who had received kidney transplants and had participated in a prospective randomized trial that compared a sirolimus-containing immunosuppression regimen to a tacrolimus-containing regimen. Sixteen subjects (seven with sirolimus, nine with tacrolimus) had received abdominal imaging studies within 11 mo before and at least 7 mo after transplantation, making them suitable for our analysis. Treatment with the sirolimus regimen for an average of 19.4 mo was associated with an 11.9 +/- 0.03% reduction in polycystic liver volume, whereas treatment with tacrolimus for a comparable duration was associated with a 14.1 +/- 0.09% increase. A trend toward a greater reduction in native kidney volume was also noted in the sirolimus group compared with the nonsirolimus group. Regarding mechanism, the epithelium that lines hepatic cysts exhibited markedly higher levels of phospho-AKT, phospho-ERK, phospho-mTOR, and the downstream effector phospho-S6rp compared with control biliary epithelium. In summary, treatment with sirolimus was associated with decreased polycystic liver volume, perhaps by preventing aberrant activation of mTOR in epithelial cells lining the cysts.

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