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거대간낭종을 동반한 상염색체우성 다낭신 환자에서 시롤리무스의 간낭종 성장 억제 효과

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Sirolimus for ADPKD Patients with Massive Polycystic LiVER (SILVER): A Single-center, Open-label, Single-arm Prospective Clinical Trial

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Introductions and Aims: Polycystic liver is the most common and often fatal extrarenal manifestation to autosomal dominant polycystic kidney disease (ADPKD) patients. We aimed to assess the efficacy and safety of mTOR inhibitor, sirolimus on liver cyst growth in patients with severe polycystic liver.

Methods: We designed a single-center, open-label, single-arm trial in Korea. Adult (18-65 years) ADPKD patients with massive polycystic liver (total liver volume (TLV) >2500 mL) or symptomatic polycystic liver received sirolimus (Rapamune) starting from 2 mg per day for 1 year and followed up with conventional treatment for another 1 year. Participants visited the clinic every 2 weeks for first 2 months to titrate drug dose to trough level of 4-10 ng/dL. The primary endpoint was change in TLV at 1 year measured with CT volumetry. Outcome measures were analyzed using per protocol (PP) methods. This study was registered with ClinicalTrials.gov, NCT01680250.

Results: Twelve patients (mean age 49 years old, female 83%) were enrolled between September 20, 2011 and February 4, 2013. Median TLV and TKV at baseline were 5641 mL (IQR 4849, 8128) and 1387 mL (IQR 599, 2763), and baseline eGFR was 59 mL/min/1.73m^2. Five patients (42%) dropped out due to adverse events including easy bruisability, diarrhea, proteinuria with renal progression, febrile sense, and aphthous stomatitis. Therefore, 7 patients were included in the efficacy analysis. TLV was significantly increased from 6713.3 mL to 7494.3 mL (+11.6%) after 1 year of sirolimus treatment (p=0.02). TKV was not significantly changed after treatment (2450 vs. 2537 mL, p=0.47), whereas eGFR was significantly decreased in spite of sirolimus treatment (59.1 vs. 50.8 mL/min/1.73m^2, p=0.02). Serious adverse events occurred in 2 subjects (1 death from biliary sepsis, 1 admission from cyst infection). Two patients intermittently reduced or stopped study medication because of adverse events (cyst infection and increased proteinuria with renal progression). The high rate of adverse events prompted us to stop further enrollment for safety reason.

Conclusions: Sirolimus did not effectively reduce TLV in ADPKD patients with massive or symptomatic polycystic liver.

Key Words: 상염색체우성다낭신, 간낭종, 시롤리무스
ADPKD, Polycystic Liver, Sirolimus