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Efficacy of 4 Years of Octreotide Long-Acting Release Therapy in Patients With Severe Polycystic Liver Disease

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Abstract

Objective: To observe the effect on total liver volume (TLV) on and off therapy in selected symptomatic patients with autosomal dominant polycystic kidney disease (ADPKD) or autosomal dominant polycystic liver disease (PLD) who received octreotide long-acting release (OctLAR) for up to 4 years.

Patients and Methods: Twenty-eight of 42 participants in a prospective 2-year clinical trial of OctLAR (40 mg monthly) consisting of double-blind, randomized (year 1) and open-label treatment (year 2) phases reenrolled in a 2-year open-label extension (OLE) study after being off OctLAR a mean of 8.3 months (original study: July 1, 2007, through June 30, 2013). Participants underwent magnetic resonance imaging at baseline, years 1 and 2, reenrollment, and study completion. Primary end point: change in TLV; secondary end points: changes in total kidney volume, glomerular filtration rate, quality of life (QoL), safety, vital signs, and laboratory parameters.

Results: Twenty-five participants (59.5%) completed the OLE. Off therapy, TLVs increased a mean ± SD of 3.4%±8.2% per year; after resuming therapy, TLVs decreased a mean ± SD of −4.7%±6.1% per year. Despite regrowth off treatment, overall reductions were observed, with a median (interquartile range) TLV of 4047 mL (3107-7402 mL) at baseline and 3477 (2653-7131 mL) at study completion (−13.2%; $P<.001$) and with improved health-related QoL. Total kidney volumes increased, and glomerular filtration rates declined from 58.2 mL/min to 54.5 mL/min (n=16) in patients with ADPKD on therapy from baseline to study completion.

Conclusion: Therapy with OctLAR over 4 years in selected patients with symptomatic PLD arrested PLD progression, alleviating symptoms and improving health-related QoL. Discontinuation led to organ regrowth.

Trial Registration: clinicaltrials.gov Identifier: NCT00426153.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease and is characterized by the development of kidney cysts and progressive kidney function loss, often leading to end-stage renal disease. The liver is the most common extrarenal site of involvement.[1] Mutations in 1 of 2 genes, *PKD1* and *PKD2*, can lead to this disease. Another disease, autosomal dominant polycystic liver disease (PLD), leads to a similar liver cystic phenotype and no renal failure. There are currently no Food and Drug Administration–approved treatments for either disease capable of attenuating the rate of cyst formation. However, several clinical trials with somatostatin analogs have shown short-term benefit in the symptomatic PLD associated with these disorders.[2-4] We previously completed a double-blind, randomized, placebo-controlled clinical trial using octreotide long-acting release depot (OctLAR) (Novartis Pharmaceuticals Corporation) over 2 years in 42 patients with severe PLD due to autosomal dominant PLD or ADPKD.[5,6] A relatively small, prospective, randomized clinical trial with 3 years of follow-up in patients with ADPKD focused on the renal but not the hepatic manifestations of the disease.[7] Two other prospective clinical trials have shown

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similar positive effects of somatostatin analogs in autosomal dominant PLD and ADPKD.[2-4,8] One of these, a 12-month trial of somatostatin analog therapy, extended follow-up another 6 months in an open-label extension (OLE) study.[9] A few other published reports relating to the use of somatostatin analogs further substantiate these observations.[8,10,11]

To evaluate whether long-term therapy retards liver growth beyond 2 years, the protocol design included a further 2-year OLE with OctLAR. Herein, we report the effects of OctLAR in patients treated for up to 4 years who were randomized in the original study and the effects of therapy discontinuation after the first 1 to 2 years of treatment.

PATIENTS AND METHODS

This is a 2-year OLE study of patients with severe PLD who had completed a clinical trial consisting of a 1-year, randomized, placebo-controlled, double-blind study of OctLAR with 2:1 randomization and a second-year open-label treatment study of all participants with OctLAR. The rationale, design, eligibility criteria, and implementation of the original trial have been described elsewhere.[5,6] The Mayo Clinic Institutional Review Board approved this study, and it was conducted in adherence with the Declaration of Helsinki. All the authors had access to the study data and reviewed and approved the final manuscript.

Severe PLD was defined as a liver volume greater than 4000 mL or symptomatic disease due to mass effects from hepatic cysts.

All participants who completed the original 2-year clinical trial were offered participation in the 2-year OLE except those who had reached advanced stage 4 or 5 chronic kidney disease. After completion of the original clinical trial, participants were off therapy for a mean of 8.3 months (mean, 249 days; median, 306 days; range, 0-442 days) before starting the OLE. Original trial enrollment took place from January 1, 2007, through May 19, 2008, and patients reenrolled in the 2-year OLE from January 1 through July 31, 2010. All patients enrolling in the 2-year OLE signed an informed consent form and were evaluated by the principal investigator (M.C.H.) or a co-investigator (V.E.T.) every 6 months during the OLE. Evaluations included physical examination, vital signs, and laboratory parameters (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, electrolytes, blood urea nitrogen, creatinine, fasting glucose, complete blood cell count, activated partial thromboplastin time, and prothrombin time). On reenrollment, all women of childbearing age had a pregnancy test, and all patients were required to use contraception or were postmenopausal. Magnetic resonance imaging (MRI) or computed tomography (CT) of the liver and kidneys was performed at reenrollment in the OLE ($OLE_{baseline}$) and at the end of year 4 (OLE_{end}). Three monthly telephone follow-up monitoring visits were made by a study coordinator or as needed when there were adverse events. If drug adverse effects were identified during a telephone visit, a decision was made by the study team to reduce the next injection dose by 10 or 20 mg. The OctLAR was dispensed at 4-month intervals by the Mayo Research Pharmacy during the OLE.

The main goal of the OLE study was to analyze the change in total liver volume (TLV). Additional goals were to assess the effects of OctLAR on total kidney volume (TKV), glomerular filtration rate (GFR) as measured by iothalamate clearance, and quality of life (QoL), as well as its safety and toxicity. Liver volume was measured by MRI (or CT in 2 patients) at $OLE_{baseline}$ and OLE_{end} (eg, after up to 4 years of treatment) and was compared with the baseline, 12-month, and 24-month measurements of the original trial. The TKV, estimated GFR (eGFR), QoL as measured by the 36-item Short-Form Health Survey Version 2.0, safety as ascertained by reported adverse events, vital signs, and laboratory tests were measured at the same time points. Adverse effects were classified by Common Terminology Criteria for Adverse Events version 3. The study coordinator confirmed monthly drug and dose administration.

Acquisition of MRIs and CT scan at $OLE_{baseline}$ and OLE_{end} was performed using the protocol as described in the previous clinical trial.[5,6] The TLVs and TKVs were measured blindly (M.V.I.) in the Imaging Core of the Mayo PKD Translational Center as previously described.[5,6] The comparability of volumetric measurements from MRI and CT and the low interobserver variability have been previously established.[6] Absolute TLV and TKV at $OLE_{baseline}$ and OLE_{end} were compared with baseline, year 1, and year 2