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CLINICAL—LIVER

Young Women With Polycystic Liver Disease Respond Best to Somatostatin Analogues: A Pooled Analysis of Individual Patient Data

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This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this CME exercise, successful learners will be able to select polycystic liver disease patients for somatostatin analogue therapy.

See editorial on page 279.

BACKGROUND & AIMS: Clinical trials have shown that in patients with polycystic liver disease (PLD), short-term treatment with somatostatin analogues (SAs) reduces liver volumes by 4.5%−5.9%, compared with placebo. However, the effects of SA therapy vary among individuals. We collected data from individual patients with PLD to identify subgroups that benefit most from SA therapy. **METHODS:** We analyzed data from 107 patients with PLD from 3 randomized placebo-controlled trials (67 received SAs, 52 received placebo). We used multiple linear regression analysis to determine the effects of SAs based on patients' age, sex, baseline liver volume, and diagnosis (autosomal dominant polycystic liver or kidney disease). The primary outcome was change in liver volume after 6−12 months of treatment. **RESULTS:** The effects of SA therapy did not differ significantly among patients with different diagnoses or baseline liver volumes; the overall difference in liver volume between groups receiving SAs therapy vs placebo was 5.3% ($P < .001$). Among subjects given placebo, young women (48 years old or younger) had the greatest increase in polycystic liver volume (4.8%; 95% confidence interval: 2.2%−7.4%), and mean liver volumes did not increase in older women and men. Women 48 years old or younger had a greater response to therapy (a reduction in liver volume of 8.0% compared with placebo; $P < .001$) than older women (a reduction in liver volume of 4.1% compared with placebo; $P = .022$). **CONCLUSIONS: Based on a pooled analysis of data from individual patients with PLD, treatment with somatostatin analogues is equally effective for patients with autosomal dominant polycystic kidney disease or polycystic liver disease; efficacy does not depend on size of the polycystic liver. Young female patients appear to have the greatest benefit from 6−12 months of SA therapy, which might avert the progressive course of the disease in this specific group.**

Keywords: Liver Cysts; PCLD; ADPKD; Drug Therapy.

Polycystic liver disease (PLD) is characterized by the progressive formation of multiple fluid-filled cysts throughout the liver, requiring liver transplantation in severe cases.[1,2] Polycystic livers are the primary presentation in isolated autosomal dominant polycystic liver disease (PCLD), and can manifest as an extrarenal manifestation in autosomal dominant polycystic kidney disease (ADPKD).[3−6] Current available treatment options are mainly surgical and aim at reducing liver volume to ameliorate mechanical symptoms.[7−9] Although these surgical procedures are effective in selected patients, the morbidity rate and their inability to alter the natural course of this disease highlights a clear need for new therapeutic options.

Somatostatin analogues (SAs), such as lanreotide, octreotide, and pasireotide, are thought to decrease polycystic liver volume by curtailing cyclic adenosine monophosphate production in hepatic cysts.[10,11] After a randomized, placebo-controlled, clinical trial (RCT) showing that 6-month long-acting octreotide safely slowed renal volume expansion in ADPKD patients, 3 RCTs demonstrated that the efficacy of long-acting lanreotide or octreotide therapy reversed liver volume

Abbreviations used in this paper: ADPKD, autosomal dominant polycystic kidney disease; CI, confidence interval; CT, computed tomography; IPD, individual patient data; PCLD, autosomal dominant polycystic liver disease; PLD, polycystic liver disease; RCT, randomized controlled trial; SA, somatostatin analogue.

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growth in PLD patients.[12–15] All trials demonstrated similar responses, with treatment effects of −4.5% to −5.9% in liver volume when compared with placebo.[16]

However, the treatment effect of SAs in these RCTs varied greatly among individual patients, ranging from gains of 300 mL to losses of 1500 mL in liver volume. In addition, results from 2 trials suggested those with larger polycystic livers had greater reductions in liver volume than those with smaller volumes.[13,14] Risk factors for liver cyst growth are age and female sex, which suggest that these might also impact treatment response to SAs.[17,18] Finally, one trial reported similar effects of SA therapy in ADPKD and PCLD patients, but this trial lacked power to make final conclusions.[14] Collectively, these findings suggest that treatment responsiveness can be increased in specific subgroups of PLD patients.

Unfortunately, the relatively small number of patients and the specific patient characteristics has precluded any meaningful subgroup analyses within each of these individual RCT. Study level meta-analyses are adequate when estimating a single pooled treatment effect, but are limited in explaining heterogeneity, and do not relate effects of therapy to the single patient. To overcome these limitations and increase statistical power, we performed an individual patient data (IPD) pooled analysis using data from all available placebo-controlled randomized trials and investigated whether the efficacy of SAs is affected by patient factors. Therefore, the aim of the current IPD pooled analysis was to estimate the effect of SAs on polycystic liver volume in PLD subgroups based on underlying diagnosis, sex, age, and liver size, to identify patients that respond best to therapy.

Materials and Methods

Literature Search

We performed a systematic literature search in the following electronic databases: PubMed (Medline), Cochrane Controlled Trials Register (CENTRAL), clinical trials.gov, and Web of Science from January 2000 until July 2012. The keywords *polycystic liver*, *ADPLD*, *PCLD*, or *ADPKD* and *somatostatin*, *SA*, *lanreotide*, *Somatuline*, *octreotide*, *Sandostatine*, or *pasireotide*, and *placebo* were combined.

Study Selection

We included all studies that were randomized, published as full articles or as an abstract, compared the effect of SAs with placebo in adult PCLD or ADPKD patients with a polycystic liver, and reported change in polycystic liver volume as the primary end point. Searches were limited to English, Dutch, or German language. Only trials for which we obtained the actual data were included in the analysis. Authors were contacted for additional information in case the methodological quality of a trial was not adequately described in the original article. An additional search was performed using the references of all included trials to retrieve eligible studies possibly missed by our systematic literature search.

Data Abstraction

We sent an electronic form containing the data fields to be completed for individual patients to all principal investigators of the trials. Two authors (Tom J. G. Gevers and Joanna IntHout) who had not participated in any of the included RCTs pooled and analyzed all patient data. Subsequently, they checked databases for completeness and internal consistency and made corrections through correspondence with the investigators. The risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[19] The following domains were included for assessment of risk of bias: sequence generation, allocation concealment, blinding (masking) of participants, personnel and outcomes assessors, description of the completeness of outcomes data for each main outcome, assessment of selective reporting, and other sources of bias specific to the study. Authors were contacted for additional information in case the methodological quality of a trial was not adequately described in the original article.

Outcomes

The primary outcome was change in liver volume as calculated by computed tomography (CT) or magnetic resonance imaging volumetry. The methods of volumetry are presented in detail elsewhere.[12–14,20,21] As liver volumes were measured at different follow-up time points, we aggregated the data at 6 months and 12 months of follow-up. Secondary outcomes were safety, tolerability, and fasting plasma glucose levels, as glucose intolerance is a common side effect of SA therapy. Patient subgroups included in the IPD pooled analysis were underlying diagnosis (ADPKD or PCLD), sex, age, and baseline liver volume. ADPKD was diagnosed in cases where >5 kidney cysts in either one or both kidneys were visible on CT; otherwise patients were diagnosed with PCLD. The age of the patient was assessed at baseline CT or magnetic resonance imaging.

Statistical Analysis

The IPD pooled analysis was conducted according to the intention-to-treat principle as described in the original articles.[12–14] As liver volumes have a skewed distribution, we first calculated the logarithms of liver volumes and then carried out the analyses. The treatment effect estimates were backwards transformed and the results were presented as mean percentage differences between SA and placebo, with 95% confidence intervals (CI). In the pooled analysis, we estimated the overall treatment effect of SAs on liver volume, using linear regression analysis with independent variables treatment group (SA or placebo); the logarithm of baseline liver volume; and patient characteristics of sex, age, and underlying diagnosis (APDKD/PCLD). We included the variable study as a fixed effect to take into account the heterogeneity among the different studies, which also included adjustment for differences in length of follow-up (6 vs 12 months). Because one of the trials had a cross-over design, we also included the individual patient as a random factor. For the primary objective, we evaluated the effect of SAs in subgroups by calculating interactions between treatment group (SA or placebo) and possible effect modifiers (diagnosis, sex, age, and logarithm of baseline liver volume). For this purpose, we added each interaction term (treatment group × potential effect modifier) separately to the main model. As multiple factors can affect growth of liver cysts, patients with more

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