Somatostatin, Estrogen, and Polycystic Liver Disease

In this issue of GASTROENTEROLOGY, Gevers et al 1 describe a gender difference in the response of polycystic liver disease (PCLD) to treatment with somatostatin analog. Men do not respond, but women, particularly young women (≤48 years of age), do! What is the rationale and role for somatostatin analog therapy in the treatment of PCLD? Why do women respond differently than men?

PCLD and Female Gender

There are 2 forms of polycystic liver, one occurring in isolation (isolated PCLD), and the other in association with renal cystic disease (autosomal-dominant polycystic kidney disease [ADPKD]). Mutations in the PKD1 and Sec63 genes are responsible for PCLD and mutations in the PRKCSH and PKD2 genes are responsible for ADPKD. The proteins produced by these genes interact at multiple intracellular levels and influence several pathways regulating fluid secretion and proliferation of biliary and cyst epithelial cells (Figure 1).

The prevalence of hepatic cysts increases with age, and the number and size of hepatic cysts is related to female gender, use of contraceptive steroids, pregnancy, and use of postmenopausal estrogen replacement therapy.2

Rationale for Somatostatin Analog Therapy

Hepatic cystic epithelium is derived from cholangiocytes, and both cholangiocyte proliferation and secretion are regulated by adenosine 3′,5′-cyclic monophosphate (cAMP). Masyuk et al 3 demonstrated that cAMP levels were 2-fold elevated in the serum and cholangiocytes of rats with PKD, a rodent model of polycystic disease. They showed that somatostatin receptor (SSTR) subtypes that bind octreotide (SSTR-2, -3, and -5) were present in both normal and PKD cholangiocytes. In addition, administration of octreotide to PKD rats reduced cAMP levels by 32%–39% and inhibited hepatic disease progression by 22%–60% as measured by liver weight, cyst volume, hepatic fibrosis, and mitotic indices.

Clinical Trials

Van Keimpema et al 4 conducted a double-blind, controlled trial of 54 patients randomized to receive either lanreotide, 120 mg SQ, or matched placebo (normal saline SQ), every 28 days for 6 months. Patients treated with lanreotide experienced a 2.9% reduction in total liver volume and patients treated with placebo experienced a 1.6% increase in liver volume (P < .01). Perhaps the most striking observation was the marked variability in individual responses. Nearly all the patients with more than a 100-mL absolute increase in total liver volume were treated with placebo. In contrast, nearly all the patients with more than a 100-mL absolute decline in total liver volume were treated with lanreotide. One quality-of-life measure, current health perception, improved in patients taking lanreotide (P < .01). The results from this trial were encouraging regarding a potential role for lanreotide in the medical treatment of polycystic liver disease.

All patients enrolled in this above trial were then offered open-label treatment with lanreotide for ≤12 months total.5 A total of 41 of the 54 patients participated. The overall decline in total liver volume was 4%, with virtually all of the reduction in volume occurring within the first 6 months of treatment. Liver volume remained unchanged during the last 6 months of treatment. Twenty-two patients had total liver volume determined 6 months after the end of the 1 year of lanreotide.

Disappointingly, liver volume increased 4%, essentially back to baseline!

Caroli et al. used a cross-over design to study 6 months of treatment with octreotide long-acting release (LAR; 40 mg IM every 4 weeks) in 12 ADPKD patients with moderate hepatic cystic disease. In a post hoc analysis of liver volume, patients treated with octreotide experienced a 4.5% reduction in total liver volume (mean change, –71 mL; mean base volume, 1595 mL). In contrast, patients taking placebo had a 0.9% increase in total liver volume (mean change, +14 mL; mean base volume, 1580 mL). The authors reported no side effects or adverse events related to octreotide.
Hogan randomly assigned 42 patients with ADPKD or PCLD to either octreotide LAR (≤40 mg every 28 days) or placebo for 1 year. Total liver volume decreased by 4.95% in the patients treated with octreotide, compared with an increase of 0.92% in patients taking placebo ($P = .045$). Patients on octreotide reported improvements in physical activity ($P < .04$) and bodily pain ($P < .02$). More than one half of the patients treated with octreotide experienced mild diarrhea. Two patients had preexisting gallbladder disease that did not worsen with treatment; 1 patient each experienced alopecia and bradycardia. Plasma glucose levels during octreotide increased 10%, compared with 2% with placebo ($P < .02$), but no patient developed diabetes mellitus.

All patients enrolled in this trial were offered an additional 1 year of treatment with open-label octreotide LAR. A total of 41 of the 42 patients participated. Patients who were initially treated with placebo experienced a 7.66% decline in total liver volume after 1 year of octreotide treatment ($P = .011$). Patients who previously received 1 year of octreotide failed to demonstrate any further decline in total liver volume during a second year of treatment (mean change, $-0.77%$; $P =$ NS). In pooled analysis, the average reduction in total liver volume after 1 year of octreotide LAR was 6.08% ($P = .001$). Patients treated with octreotide reported improvement in physical role ($P = .0031$), bodily pain ($P = .0035$), or vitality ($P = .0022$). One patient withdrew owing to steatorrhea and weight loss; 28% of patients experienced diarrhea and 58% had injection site reactions. One patient with preexisting gallbladder disease developed acute cholecystitis requiring cholecystectomy.

### Gender Effect in Response to Somatostatin Analog

The current *GASTROENTEROLOGY* article is an analysis of pooled data from the 3 randomized trials described. The goal was to identify the subgroup of patients who could derive the greatest benefit from treatment with somatostatin analog. The analysis included 107 patients, 67 of whom received somatostatin analogs. The variables of age, gender, baseline liver volume, and diagnosis (ADPKD vs PCLD) were included in the models and primary outcome was the change in total liver volume after 6-12 months of treatment. There was a striking difference in response related to gender—men failed to respond, but women and particularly younger women responded. Young women ($≤48$ years of age) demonstrated an 8.0% reduction in total liver volume ($P < .001$), whereas older women ($>48$ years of age) experienced a 4.1% reduction in total liver volume ($P = .022$). Response was not related to baseline liver volume or underlying form of polycystic liver (ADPKD vs PCLD).

The basis for the increased responsiveness in women is unknown. However, an enhancing effect of estrogen on the response to somatostatin has been described for pituitary tumors and other conditions. The mechanism may be related to estrogen-induced modification of intracellular signaling pathways, such as JAK-STAT, ERK, or AP1.

### When Is Treatment With Somatostatin Analog Indicated?

Any conclusion regarding use of somatostatin analogs in the treatment of PCLD must be tempered by the fact that the total treatment experience encompasses a very small number of patients. Nonetheless, the results across studies are reasonably similar. Treatment is associated with an initial decline in liver volume of about 4%-6% and is associated with improvement in some measures of quality of life. However, continued treatment beyond 6 or 12 months provides little, if any, further reduction in total liver volume. Once stopped, total liver volume rebounds toward baseline. This would imply that long-term maintenance therapy would be required.

The modest clinical benefits, side effects (diarrhea, increased glucose, risk for gallbladder disease) and cost do not permit a general recommendation for use of somatostatin analogs in PCLD. This therapy seems to be ineffective in men, modestly effective in older women, and most effective in younger women. Perhaps treatment should be targeted toward women, especially younger women, with extensive hepatic cystic disease and symptoms. If treatment is initiated, continuation of treatment should be, contingent on demonstrating a significant reduction in total liver volume and resolution of symptoms after 6 months of treatment. The data suggest that a nonresponder after 6 months of treatment is not likely to achieve reduction in liver volumes or improvement in symptoms with continued treatment.

### Future Medical Options

More effective drugs are needed if medical therapy is to replace cyst aspiration and sclerosis, cyst fenestration via laparoscopy or open laparotomy, hepatic resection, and liver transplantation. Clearly, the latter treatments are suboptimal and associated with significant morbidity, high costs, high rates of recurrence, and even death. Effective medical therapy would be widely embraced by patients, care providers, and their physicians.

There are 5 SSTRs, SSTR-1 to -5, and each has different affinity for somatostatin, octreotide, lanreotide, and pasireotide. In the PKD rat model, pasireotide, a more potent somatostatin analog with broad receptor specificity, was significantly more effective in reducing hepatic cystogenesis than octreotide. These studies suggest that clinical trials of more potent somatostatin analogs, such as pasireotide, may be warranted.

The mammalian target of rapamycin (mTOR) regulates secretion and proliferation of biliary and cystic epithelium.
An observational study showed reduction in liver volume during rapamycin (sirolimus)-based immunosuppression in renal recipients with ADPKD and hepatic cysts. However, a randomized, controlled trial of patients with either ADPKD or PCLD failed to demonstrate a benefit of everolimus when added to octreotide LAR. The lack of efficacy coupled with the side effects of everolimus has reduced the enthusiasm for use of mTOR inhibitors.

In conclusion, current somatostatin analogs have a limited role in treating PCLD. The authors agree that “further large-scale multicenter studies evaluating the long-term effects of somatostatin analogs on liver volume and symptom resolution in PLD patients are necessary to substantiate the merits of this therapy.” Studies of somatostatin in combination with estrogen (or related compounds) on biliary and cyst epithelial function may yield new therapeutic targets.

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Obesity Heats Up Adipose Tissue Lymphocytes


A major advancement in obesity research over the past decade is the framing of obesity as a chronic inflammatory state. The nature of this inflammation is unique compared with classical inflammatory responses employed in host defense and pathogen recognition and has dramatic impacts on the metabolic control of nutrient flow. This “meta-inflammation” is low grade, long lasting, and enhanced in many metabolic tissues important in regulation of dietary nutrients, such as liver, muscle, pancreas, and adipose tissue. The cellular components of meta-inflammation include mediators of both innate and adaptive immunity and grow more diverse by the day. A study by Fabbri et al in this issue of GASTROENTEROLOGY advances our understanding of how interleukin (IL)-17-producing CD4+ lymphocytes may contribute to obesity-associated disease and provides a new perspective on the pathways that fan the flames of inflammation associated with metabolic disease.

Obesity generates a range of cellular stress in hypertrophic adipose tissue as well as in the fatty liver. Tissue leukocytes seem to respond directly to this stress, likely as a homeostatic mechanism to return the system to a