Milk Thistle for Alcoholic or Hepatitis B or C Liver Disease

Randomized clinical trial studies in patients with alcoholic and/or hepatitis B and C liver disease were included in the assessment. Randomized clinical trials were evaluated by components of methodologic quality. Thirteen randomized clinical trials assessed milk thistle (MT) in 915 patients with alcoholic and/or hepatitis B or C liver diseases. The methodologic quality was low; only 23 percent of the trials reported adequate allocation concealment and only 46 percent were considered double-blind. MT versus placebo or no intervention for a median duration of 6 months had no significant effect on all cause-mortality complications of liver disease or liver histology. Liver-related mortality was significantly reduced by MT in all trials, but not in high-quality trials. MT was not associated with a significantly increased risk of adverse events.

Based on high-quality trials, MT does not seem to significantly influence the course of patients with alcoholic and/or hepatitis B or C liver disease. MT could potentially effect liver injury. Adequately controlled clinical trials with MT versus placebo may be needed. (Rambaldi A, Jacobs B, Iaquinto G, et al. “Milk Thistle for Alcoholic and/or Hepatitis D or C Liver Disease—A Systematic Cochrane Hepato-Biliary Group Review with Meta-Analyses of Randomized Clinical Trials.” Amer J Gastroenterol, 2005; Vol. 100, 2583-2591.)

Treatment of Hepatitis C in Children

The evaluation of the efficacy, safety and pharmacokinetics of Interferon Alfa-2a and Ribavirin in children with chronic hepatitis C was carried out. The optimal Ribavirin dose was used after identified, in combination with Interferon and Alfa-2B, finally in a phase 3 trial. The primary efficacy end-point in all studies was sustained virological response, defined by undetectable serum HCV RNA 24 weeks after completion of therapy. All efficacy and safety analyses were performed on the intent-to-treat population. Children receiving Interferon Alfa-2B plus Ribavirin 15 mg/kg in the phase one study had the maximum reduction in serum HCV RNA at treatment, weeks 4 and 12, with an acceptable safety profile.

In all, 46 percent (54/118) of optimally treated children achieved sustained virological response. That response was significantly higher in genotype 2/3 (84 percent), than in those with genotype 1 (36%). Adverse events led to dose modification in 31 percent and discontinuation in 7 percent. Multiple-dose Interferon Alfa-2B and Ribavirin peak and trough concentration and area-under-the-curve were similar between children and adults.

In conclusion, Interferon Alfa-2B in combination with Ribavirin is effective and safe in children with chronic hepatitis C viral infection. (Gonzalez-Peralta RT, Kelly DA, Haber B, et al, for the International Pediatric Hepatitis C Therapy Group. Hepatology, 2005; Vol. 42, 1010-1018.)

Entecavir and Lamivudine-Refractory HBV

A randomized dose-ranging, phase 2 study compared the efficacy and safety of Entecavir with Lamivudine in Lamivudine-refractory patients. Hepatitis Be antigen positive and negative patients (182), viremic displayed Lamivudine treatment for 24 or more weeks, or having documented Lamivudine resistant substitutions, were switched directly to Entecavir (1, 0.5 or 0.1 mg daily), or continued on Lamivudine 400 mg daily for up to 76 weeks.

At week 24, significantly more patients receiving Entecavir 1 mg (79%), or 0.5 mg (51%), had undetectable HBV DNA levels by branched chain assay, compared with Lamivudine (13%).

Entecavir 1mg was superior to 0.5 mg for the standard point. After 48 weeks, a mean reduction in HBV DNA levels was 5.86, 4.46 and 2.85 log_{10} copies/mL. Entecavir 1 mg, 0.5 mg and 0.1 mg, respectively was significantly higher than 1.37 log_{10} copies/mL on Lamivudine. Significantly higher proportion of patients achieved normalization of ALT on Entecavir (continued on page 88)
than on Lamivudine. One virologic resistance occurred in the 0.5 mg group.

It was concluded that in HbeAg-positive and HBeAg-negative Lamivudine refractory patients treated with Entecavir 1mg and 0.5 mg daily was well tolerated and resulted in significant reduction in HBV DNA levels and normalization of ALT. 1mg of Entecavir was considered more effective than 0.5 mg in this population. (Chang TT, Ishi RG, Hadzaynnis J, et al. for the BEHoLZ Study Group. Gastroenterology, 2005; Vol. 129, pp. 1198-1209.)

Steatosis and Hemochromatosis

Two hundred fourteen patients with hemochromatosis who were homozygous with C282Y substitution HFe, and who had undergone liver biopsy prior to phlebotomy were studied. Steatosis was present in 41.1 percent of patients. Fourteen percent had moderate or severe steatosis. Median serum ALT and ferritin levels were higher and median transferrin saturation, and hepatic iron concentration were lower in subjects with steatosis, compared with subjects without steatosis. Bivariate analysis revealed a significant association with steatosis and fibrosis. Following multiple logistic regression, steatosis was independently associated with fibrosis, along with male sex, excess alcohol consumption and hepatic iron content. Note: higher BMT and alcohol consumption was associated with the presence of steatosis.

It was concluded that these findings indicate that obesity-related steatosis may have a role as a cofactor in liver injury in hemochromatosis. There is an important clinical implication that suggests that obesity should be actively addressed for management of patients with hemochromatosis, as well as other liver diseases. (Powell A, Clauston AG, et al. “Steatosis in a Co-Factor in Liver Injury Hemochromatosis.” Gastroenterology, 2005; Vol. 129, 1937-1943.)

Clostridium Difficile and Acid Suppression

A two population-based, case-controlled study using the United Kingdom General Practice Research Database was conducted. Sixteen hundred seventy-two cases of C. difficile reported between 1994 and 2004 were identified among all patients registered for at least 2 years in each practice. Each case was matched to ten controls on calendar time and the general practice. In the second study, a subset of these cases defined as community-acquired (i.e., not hospitalized in the prior year), were matched on practice and age with controls also not hospitalized in the prior year.

The outcome measured the incidence of C. difficile and risk associated with gastric acid-suppressive agent use. The incidence of C. difficile in patients diagnosed by their general practitioners increased from less than one case per 100,000 in 1994 to 22 per 100,000 in 2004. The adjusted rate ratio of C. difficile-associated disease with current use of proton pump inhibitors was 2.9 and with H2-receptor antagonists, the rate ratio was 2.0. An elevated rate was also found with the use of NSAIDs at 1.3.

It was concluded that use of acid-suppressive therapy, particularly proton pump inhibitors, is associated with an increased risk of community-acquired C. difficile. The unexpected increase in risk with NSAIDs will require further investigation. (Dial S, Delaney JAC, Barkan-Suiss AS.” Use of Gastric Acid-Suppressive Agents and the Risk of Community-acquired Clostridium Difficile-Associated Disease.” JAMA, 2005; Vol. 294: 2989-2995.)

Four Day Bravo pH Capsule Monitoring

Eighteen patients underwent four-day ambulatory pH testing, using two separate receivers calibrated to a single Bravo pH capsule. Rabeprazole was administered on days 2 to 4 of the study (20 mg orally b.i.d.). Indications for pH testing were refractory heartburn, chest pain or chronic cough. A pH recording showed that 9 patients (53 percent), had esophageal acid exposure values that exceeded 4 percent on day 1 and 7 patients (41 percent) had values that exceeded 5.3 percent.

Patients showed significant and progressive reductions in acid exposure on days 2 to 4 of the reported period. Of the 7 patients with quantitatively abnormal levels of acid exposure on day 1, 86 percent had normalization by day 3.
It was concluded that prolonged esophageal pH recordings using the Bravo system are feasible and allow for combined testing, both off and on a therapeutic trial of PPI. Such studies may allow for the acquisition of complementary information in a single test and may be useful in the management of patients with suspected gastroesophageal reflux disease symptoms. (Hirano I, Vang Q, Pandolfino JE, Kahrilas PK. “Four Day Bravo pH Capsule Monitoring, With and Without Proton Pump Inhibitor Therapy.” Clin Gastroenterol Hepatol, 2005; Vol. 3,1083-1088.)

Ascites, Impaired Gastric Function and Nutritional Intake

Patients with cirrhosis and ascites underwent assessment of gastric volumes as measured by single-photon computed tomography, gastric sensation assessed by a validated nutrient drink test and a 3-day assessment of caloric intake before and after large volume paracentesis.

Paired Wilcoxon rank-sum tests were used to compare gastric measure before and after paracentesis among the patient group. Fifteen patients were compared with 112 healthy controls. Median postprandial gastric volumes and gastric accommodation were reduced significantly in patients compared with healthy controls. After paracentesis, fasting gastric volumes were increased. Patients tolerated ingestion of large and maximum volumes and caloric intake was increased.

It was concluded that postprandial gastric volumes and accommodation ratios are reduced in patients with cirrhosis and ascites, compared with healthy controls. Large volume paracentesis increase fasting gastric volume; volumes suggested a total maximum satiation and caloric intake. (Aqel BA, Scolapio JS, Dickson RC, Burton DT, Bouras EP. “Contribution of Ascites to Impaired Gastric Functional and Nutritional Intake in Patients With Cirrhosis and Ascites.” Clin Gastroenterol Hepatol, 2005; Vol. 3, 1095-1100.)

Treatment of Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy is characterized by troublesome maternal pruritus, elevated serum bile acids and increased fetal risk. It has been determined that a cutoff level of serum bile acids equal to or greater than 40umol/L can be associated with impaired fetal outcome. This study was carried out to evaluate the effects of ursodeoxycholic acid (UDCA) and Dexamethasone on pruritus, biochemical markers of cholestasis and fetal complication rates in a double-blind, placebo-controlled trial. One hundred thirty women with ICP were randomly allocated to UDCA (one gram per day for 3 weeks), or Dexamethasone (12 mg per day for one week and placebo during weeks 2 and 3), or placebo for 3 weeks.

Pruritus and biochemical markers of cholestasis were analyzed at inclusion and after 3 weeks of treatment. Fetal complications were registered at delivery. An intention to treat analysis showed significant reduction of ALT and bilirubin in the UDCA group only. In a subgroup analysis of ICP women with serum bile acids equal to or greater than 40 umol/L at inclusion, UDCA had significant effects on pruritus, bile acids, ALT and bilirubin, as well, but not on fetal complication rates.

Dexamethasone yielded no alleviation of pruritus or reduction of ALT and was less effective than UDCA at reducing bile acids and bilirubin.

It was concluded that three weeks of UDCA treatment improves biochemical markers of ICP, irrespective of disease severity, whereas significant relief from pruritus and marked reduction of serum bile acids were only found in patients with severe ICP. (Glantz A, Marschall H, Lammert F, Matteson L. “Intrahepatic Cholestasis of Pregnancy: A Randomized Controlled Trial Comparing Dexamethasone and Ursodeoxycholic Acid.” Hepatology, 2005; Vol. 42, 1399-1405.)

Incidence of Barrett’s Esophagus

A random sample, including 3,000 adults as a representative of the adult population (21,610) was carried out in two units. The use of Palatine was surveyed using the validated gastrointestinal symptom questionnaire. A random subset sample of 1,000 patients underwent upper endoscopy. Endoscopic signs suggested a columnar-lined esophagus (CLE) and were defined as mucosal tongues or an upward shift of the squamocolumnar junction. Barrettes esophagus (BE) was diagnosed when specialized intestinal metaplasia was detected histologically in suspected CLE.

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BE was present in sixteen subjects (1.6 percent), five with a long segment and 11 with a short segment. Overall, 40 percent reported reflux symptoms and 15.5 percent showed esophagitis; 103 (10 percent) had suspected CLE and 12 (1.2 percent) had a visible segment greater or equal to 2 cm.

The prevalence of BE in those with reflux symptoms was 2.3 percent and in those without reflux symptoms was 1.2 percent. In those with esophagitis, the prevalence was 2.6 percent. In those without the prevalence, it was 1.4 percent. Alcohol and smoking were independent risk factors for BE.

It was concluded that BE was found in 1.6 percent of the general Swedish population. In this study, alcohol and smoking were significant risk factors. Ed Note: (Sixteen patients only). (Ronkainen J, Aro P, Storz-Krubb T, et al. “Prevalence of Barrett’s Esophagus in the General Population: An Endoscopic Study.” Gastroenterology, 2005; Vol. 129, 1825-1831.)

NSAID-Induced Small Bowel Pathology
Forty healthy volunteers underwent a baseline capsule enteroscopy and fecal calprotectin test after taking Diclofenac Slow-Release 75 mg capsules b.i.d. with omeprazole 20 mg b.i.d. for gastroprotection, for a total of 14 days. Both investigations were repeated. After drug treatment, 30 subjects had increased repeat fecal calprotectin concentrations above the upper limits of normal. Capsule enteroscopy showed new pathology in 27 subjects (68%). The most common lesions were mucosal breaks, seen in 16% or 40%, which were seen to be bleeding in two (5%); reddened folds in 14 (35%). Petechiae or red spots were seen in 13 (33%). Denuded mucosa was seen in 8 (20%), with blood in the lumen, without a visualized source 3 (8%). Fifteen of the 27 subjects had more than one lesion concurrently.

It was concluded that this study provides both biochemical and direct evidence of macroscopic injury to the small intestine, 68% to 75 % of volunteers resulting from 2 weeks ingestion of Slow-Release Diclofenac. (Maiden L, Thjodleifsson S, Theodor A, Gonzales J, Bjarnason I. “A Quantitative Analysis of NSAID-Induced Small Bowel Pathology by Capsule Enteroscopy.” Gastroenterology, 2005; Vol. 128, 1172-1178.)

Infliximab Therapy for Fistulizing Crohn’s Disease
After 5 mg/kg infliximab at weeks 0, 2 and 6, a total of 282 patients were separately randomized at week 14 as responders, including a 50% reduction from baseline in the number of draining fistulas at both weeks 10 and 14, or nonresponders to receive placebo with 5 mg/kg infliximab maintenance every 8 weeks. At week 22 and later, patients who lost response could be treated with a maintenance dose 5 mg/kg higher. Data on Crohn’s disease-related hospitalizations, surgeries and procedures were compared between the three groups for responders in all randomized patients.

A total of 282 patients were randomized at week 14, of whom 195 were randomized as responders. Among patients randomized as responders, those who received

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infliximab maintenance had significantly fewer days (0.5 versus 2.5) of hospitalization. All surgeries and procedures as well as major surgeries were compared with those who received placebo maintenance.

It was concluded that in patients with fistulizing Crohn’s disease, infliximab 5 mg/kg every 8 weeks significantly reduced hospitalizations, surgeries and procedures, compared with placebo. (Lichtenstein GR, Yan S, Bala M, Blank M, Sanders BE. “Infliximab Maintenance Treatment Reduces Hospitalizations, Surgeries and Procedures in Fistulizing Crohn’s Disease.” Gastroenterology, 2005; Vol. 128, 862-869.)

**Banding and Propanolol Prophylaxis for Initial Variceal Hemorrhage**

To compare endoscopic banding with propanolol for prevention of first variceal hemorrhage, a multicenter prospective trial was carried out. Sixty-two patients with cirrhosis with high-risk esophageal varices were randomized to propanolol, titrated to reduce resting pulse by 25% or more, or banding performed monthly until varices were eradicated. This was followed up with the same schedule for a duration of 15 months. Primary end point of treatment failure was defined as a result of endoscopically-documented variceal hemorrhage or a severe medical complication requiring discontinuance therapy. The trial was stopped early after an interim analysis showed that the failure rate of propanolol was significantly higher than that of banding. Significantly more propanolol than banding patients had esophageal variceal bleeding (4/31 vs. 0/31). The difference was 12.9%.

The cumulative mortality rate was significantly higher in the propanolol than the banding group. Direct costs of care were not significantly different.

It was concluded that for patients with cirrhosis with high risk esophageal varices and no history of variceal hemorrhage, propanolol-treated patients had significantly higher failure rates, first esophageal varix hemorrhage and cumulative mortality than banding patients. (Jutaba JR, Jensen DM, Martin T, et al. “Randomized Study comparing Banding and Propanolol to Prevent Initial Variceal Hemorrhage in Cirrhotics with High Risk Esophageal Varices.” Gastroenterology, 2005; Vol. 128, 870-881.)