tTG Antibodies in Patients with Abnormal Liver Tests

Celiac disease (CD) is found in 5 to 10 percent of patients with chronically abnormal liver tests, with no obvious cause of liver disease. In this population, the efficacy of screening for CD by anti-tissue transglutaminase (anti-tTG) may be impaired by the high rate of positive anti-tTG found in chronic liver disease. To evaluate the prevalence of celiac disease and the role of anti-tTG in patients with non-viral, non-autoimmune, chronic and no obvious cause of liver damage, 2,512 consecutive patients with abnormal liver tests were reviewed. One hundred sixty-eight were defined on the basis of clinical data at liver biopsy as NAFLD or cryptogenic chronic hepatitis. All were tested by recombinant IgA and IgG anti-tissue transglutaminase. Patients with a positive serology underwent endoscopy with duodenal biopsies.

Anti-tTG were positive in 20 of 168 patients, 3 with IgA alone, 11 with IgG alone and 6 with both. Celiac disease was found at endoscopy and confirmed by histopathology, only in the 6 patients with both IgA and IgG anti-tTG positivity for the patients with CD and NAFLD (3.3 percent), and two of them associated with cirrhosis, while two of those with cryptogenic hepatitis (4.2 percent) had CD.

The prevalence of CD in patients with chronically abnormal liver tests of unexplained etiology is 4 percent, with no relation with the degree of liver steatosis. Screening should be done by testing for IgA and IgG antibodies and then evaluated by endoscopy and biopsy, only in patients positive for both. (Iacono OL, Petta S, Venezia G, et al. “Anti-Tissue Traneglutaminase Antibodies in Patients With Abnormal Liver Tests: Is it Always Celiac Disease?” Amer J Gastroenterol, 2005; Vol. 100, 2472-2477.)

IFN and Lamivudine Combination Vs. Lamivudine Monotherapy in Hepatitis B

Monotherapy with Interferon (IFN) or Lamivudine is effective in a limited proportion of chronic hepatitis B (CHB) patients. A sequential combination was compared as to efficacy versus Lamivudine monotherapy alone in HBeAg positive CHB patients.

Seventy-five treatment-naive HBeAg positive patients with histologically-proven CHB and ALT greater than 1.5 × the upper limits of normal received Lamivudine 100 mg q.d. for 52 weeks with IFN 5,000,000 i.u./day added for 16 weeks after the first 8 weeks, or Lamivudine 100mg q.d. for 52 weeks. Biochemical and virologic responses were assessed at weeks 52 and 76 and analysis was done on an intention-to-treat. Serial samples were studied for the emergence of Lamivudine-resistant mutation direct sequencing.

At week 52, HBeAg loss occurred in 15 (39.5 percent) in group A and 14 (37.8 percent) in group B. HBeAg loss, anti-HBE appearance and undetectable DNA levels were seen in 26.3 percent and 13.5 percent, respectively. Nine of ten patients in group A and one of five patients in group B maintained a response through week 76. At week 76, five additional patients in group A and 3 in group B further achieved the end point and the overall HBeAg loss was observed in 44.7 percent and 18 percent, respectively.

HBeAg loss, anti-HBE appearance and undetectable HBV DNA levels in 36.8 and 10.8 percent in groups A and B, respectively was noted. At week 76, undetectable HBV DNA was seen at 39.5 percent and 16.2 percent in groups A and B, respectively. Normal ALT was seen in 47.7 percent and 40.5 percent at week 52. An ALT was normal in 39.5 percent and 13.5 percent at week 76 in groups A and B, respectively. Resistant mutants emerged in 6 of 38 (15.5 percent) of patients in group A and 3 of 37 (8.1 percent) in group B. The rate of histologic improvement was comparable in the two groups.

These results demonstrate that sequential therapy is superior to Lamivudine monotherapy in achieving sustained seroconversion, ALT normalization and HBV DNA loss. Compared to 80 percent with sequential therapy, only 20 percent Indian patients with CHB did not relapse after stopping Lamivudine monotherapy. (Sarin
SK, Kumar M, Kumar R, et al. “Higher Efficacy of Sequential Therapy with Interferon-a and Lamivudine Combination, Compared to Lamivudine Monotherapy in HBeAgPositive Chronic Hepatitis B Patients.” Amer J Gastroenterol, 2005; Vol. 100, 2463-2471.)

Mesalamine at 4.8 Grams Per Day in Moderately Active UC

A randomized, double-blind control trial (Ascend II) was conducted to evaluate the efficacy of 4.8 grams per day of Mesalamine in adults with active ulcerative colitis. Three hundred eighty-six patients with mild to moderate ulcerative colitis were randomized for treatment with Mesalamine 2.4 grams per day (400mg tablets) or 4.8 grams per day (800 mg tablets) for 6 weeks.

The primary end point was in proportion to patients in each treatment group that achieved overall improvement with treatment success defined as either complete remission or a clinical response to therapy from baseline at week six.

Seventy-two percent of patients receiving 4.8 grams per day for moderate ulcerative colitis received treatment success at week six, compared with 59 percent who received 2.4 grams per day. Both regimens were well-tolerated. Adverse events and clinical significant changes in laboratory results were similar in both treatment groups.

It was concluded that patients with moderately active ulcerative colitis treated with 4.8 grams per day of Mesalamine are significantly more likely to achieve overall improvement at 6 weeks, compared to patients treated with 2.4 grams per day. (Hanauer SD, Sanborn WJ, Kornbluth A, Katz S, et al. “Delayed-Release Oral Mesalamine at 4.8 Grams Per Day (800 mg Tablets) for the Treatment of Moderately Active Ulcerative Colitis: The Ascend II Trial.” Amer J Gastroenterol, 2005; Vol. 100, 2478-2485.)

Colonoscopy Vs. Angiographic Intervention with Lower GI Bleeding

Fifty consecutive patients presenting with lower gastrointestinal bleeding without upper or anorectal bleeding sources were randomized to urgent purge preparation, followed immediately by colonoscopy or a standard care algorithm, based on angiographic intervention and expectance colonoscopy.

A definite source of bleeding was found more often in urgent colonoscopy patients (diverticulosis n-13, angiectasia n-4, colitis n-4), than in the standard care group (diverticulosis n-8, colitis n-3).

The odds ratio for the difference among the groups was 2.6. In the urgent colonoscopy group, 17 patients received endoscopic therapy. In the standard care group, ten patients had angiographic hemostasis. There was no difference in outcomes among the two groups, including colon mortality (2 percent) versus 4 percent, hospital stay (5.8 versus 6.6 days), ICU stay (1.8 versus 2.4 days), transfusion requirements (4.2 versus 5 units), early rebleeding (22 percent versus 30 percent), surgery 14 percent versus 12 percent, or late rebleeding (16 percent versus 14 percent).

It was concluded that although urgent colonoscopy identified a definite source of lower gastrointestinal bleeding more often than a standard care algorithm, based on angiography and expectant colonoscopy, the approaches are not significantly different with regard to important outcomes. Decisions concerning care for patients with acute lower gastrointestinal bleeding should be based on individual experience and local expertise. (Green BT, Rockey DC, Portwood G, et al. “Urgent Colonoscopy for Evaluation and Management of Acute Lower Gastrointestinal Hemorrhage: A Randomized, Controlled Trial.” Amer J Gastroenterol, 2005; Vol. 100, 2395-2402.)

PBC Risk Factors and Comorbidities

One thousand, thirty-two patients were enrolled from 23 tertiary referral centers for liver diseases in the United States and, random digit-dialed controls (1,041) matched for sex, age, race and geographical location were also enrolled. Patients in controls were administered a modified version of the U.S. National Health and Nutrition Examination Study Questionnaire by trained personnel to evaluate associations between PBC and social, demographic, personal and family medical histories, life-style and reproductive factors and rates of comorbidity in affected individuals. Data indicates that having a first degree relative with PBC, history of urinary tract infections, past
smoking or use of hormone replacement therapies were significantly associated with increased risk of PBC. The frequent use of nail polish slightly increased the risk. Other autoimmune diseases were found in 32 percent of the cases and 13 percent of controls.

It was concluded that environmental factors, possibly including infectious agents through urinary tract infections or chemicals contained in cigarette smoke, may induce PBC in genetically-susceptible individuals. Exogenous estrogens may also contribute to explain the female predominance of the disease. (Gershwin ME, Selmi C, Warman HJ, et al, and the USA PBC Epidemiology Group. Hepatology, 2005; Vol. 42, 1194-1202.)

Steroid Injection into Recalcitrant Esophageal Strictures

Patients with peptic esophageal stricture and recurrent dysphagia, having had at least one dilation in the preceding 18 months, were enrolled in a prospective, randomized double blind study comparing steroids and sham injection. After endoscopic confirmation of recurrent stricture, patients were randomized to receive either 0.5cc/quadrant Triamcinolone (40 mg/cc) or sham injection into the stricture, followed by balloon dilatation of the stricture. Patients were stratified by the number of dilations required in the preceding 18 months, severity of dysphagia, the presence of esophagitis, stricture severity and prior severity and prior therapy with proton pump inhibitor. Patients and their physicians were blinded to the type of intervention received. Baseline dysphagia questionnaires were completed. Post-procedurally, all patients were placed on a standardized proton pump inhibitor regimen and standardized telephone follow-up questionnaires were completed at one week and at 1, 3, 6, 9 and 12 months.

A total of 30 patients were enrolled, 15 in the steroid group and 15 in the sham group. Patients were followed for one year, unless they underwent an anti-reflux operation or died. Two patients, one per group, died of nonesophageal causes and one at 12 months. Four patients had fundoplication, two in each group, unrelated to stricture or dysphagia.

Two patients in the steroid group (13 percent) and 9 in the sham group (60 percent), required repeat dilation.

It was concluded that in patients with recalcitrant peptic esophageal stricture, steroid injection into the stricture, combined with acid suppression, significantly diminishes both the need for repeat dilation and the average time for repeat dilation, compared to sham injections and acid suppression alone. (Ramage J, Rumalla A, Baron TH, et al. “A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of Endoscopic Steroid Injection Therapy for Recalcitrant Esophageal Peptic Strictures.” Amer J Gastroenterol, 2005; Vol. 100, 2419-2425.)

Anticoagulant and Antiplatelet Therapy for Endoscopic Procedures

Prospective control trials indicate that low molecular weight heparin (LMWH) and nonaspirin antiplatelet drugs are effective in the prevention and treatment of thromboembolic disease, and that nonaspirin antiplatelet drugs are associated with an increased risk of bleeding (except Dipyridamole), and that these should be discontinued in the setting of GI bleeding. It is also opined that the decision to discontinue these drugs must balance the bleeding risk against the risk of a thromboembolic event, and that for low-risk procedures, these drugs may be continued.

Furthermore, for high-risk procedures, LMWH should be discontinued at least 8 hours before the procedure.

It is opined that for Clopitogrel or Ticlopidine, there is insufficient data, but if discontinued, the drugs should be withheld for 7 to 10 days.

It was opined that LMWH may be used as a bridge for endoscopy in patients who require anticoagulation, in whom Warfarin cannot be safely discontinued.

Observational studies indicate that LMWH should not be used in pregnant women or those with mechanical prosthetic heart valves. In nonpregnant patients, short-term use of LMWH appears to be safe. However, prospective control data is lacking. (Zuckerman MJ, Hirota WK, Adler EG, et al as part of Standards of Practice Committee, American Society For Gastrointestinal Endoscopy. “ASGE Guideline: The Management of Low Molecular Weight Heparin and Non-Aspirin

(continued on page 72)

**Hepatic Toxicity from NSAIDs**
Sixty-seven articles from the bibliographic database and 65 studies from Food and Drug Administration archives met inclusion criteria in a search to identify randomized controlled trials of diclofenac, naproxen, ibuprofen, celecoxib, rofecoxib, valdecoxib, or meloxicam in adults with osteoarthritis or rheumatoid arthritis that provided information on aminotransferase elevations greater than 3 times the upper limits of normal, liver-related discontinuations, hepatic serious adverse effects, liver-related hospitalizations or liver-related deaths.

The proportion of patients with each of the hepatic toxicity outcomes were calculated separately by using samplesized, weighed pollings for each NSAID.

Diclofenac (3.5% to 5%), and rofecoxib (1.5% to 2.13%) had higher rates of aminotransferase greater than 3 times upper limits of normal than placebo, and the other NSAIDs (0.43%). Liver-related discontinuations of all NSAIDs except diclofenac overlapped with placebo. Only one liver-related hospitalization among 37,671 patients and one-liver related death among 51,942 patients occurred with naproxen.

It was concluded that diclofenac and rofecoxib had higher rates of aminotransferase elevation than placebo and other NSAIDs studied. No NSAID study had increased rates of liver related serious adverse effects, hospitalizations or deaths. (Rostom A, Goldkind L, Laine L. “Nonsteroidal Anti-inflammatory Drugs and Hepatic Toxicity: A Systematic Review of Randomized Controlled Trials in Arthritis Patients.” *Clin Gastroenterol Hepatol*, 2005; Vol. 3, 489-498.)

**Treatment Alternatives in HBV Infection**
A systematic review of med line from 1970 to 2005 was carried out, including patients with chronic HBV infections, elevated aminotransferase levels and no cirrhosis. The time horizon was lifetime and the prospective was toward the third party payor. Intervention included no HBV treatment, Interferon monotherapy, Lamivudine monotherapy, Adefovir monotherapy, or Lamivudine with crossover to add Adefovir upon resistance (Adefovir salvage strategy).

The outcome measure was incremental cost per quality-adjusted life year gained (QALY).

The do nothing strategy was least effective, yet least expensive. Using Interferon cost an incremental $6,337 to gain one additional QALY. Compared with Interferon, the Adefovir salvage strategy cost an incremental $8,446 per QALY gained. Both the Lamivudine and Adefovir monotherapy strategies were more expensive, yet less effective than the alternative strategies and were therefore dominated.

On sensitivity analysis, Interferon was most cost-effective in health care systems with tight budgetary constraints and a high prevalence of HBeAg-negative patients.

The results applied only to patients with chronic HBV infection, elevated aminotransferase levels and no clinical or histological evidence of cirrhosis. They do not apply to alternative populations.

Neither Lamivudine nor Adefovir therapy is cost-effective in chronic HBV infections. However, a hybrid salvage strategy, reserving Adefovir only for Lamivudine-associated viral resistance may be highly cost-effective across most health care settings. Interferon therapy may still be preferred in health care systems with limited resources, especially in those serving populations with a high prevalence of HBeAg-negative HBV. (Kanwal F, Gralnek IM, MartinT, et al. “Treatment Alternatives for Chronic Hepatitis B Virus Infection: A Cost-Effective Analysis.” *Ann Int Med*, 2005; Vol. 142, 821-831.)

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