PPI and Decompensated Cirrhosis

Considering that proton pump inhibitors (PPIs) may be a risk factor for hepatic encephalopathy (HE) in patients with cirrhosis, possibly through translocation of gut bacteria which can also lead to spontaneous bacterial peritonitis (SBP), the association between PPI and development of HE or SBP in patients with cirrhosis with ascites was examined.

Data from three one-year trials of satavaptan for ascites control was used with Cox regression to compare HE and SBP rates between users and nonusers of PPIs. At inclusion, 39% of the 865 patients with cirrhosis with ascites used PPIs; 52% used them at some point during the followup and the proportion of current users was always in the 30% to 39% range.

There were 189 first-time HE episodes during the follow-up and the cumulative one-year risk was 31% for those who used PPIs at baseline vs. 25% for those who do not. The confounder-adjusted Hazard Ratio (HR) of HE for current PPI use versus current nonuse was 1.36. The HR for overt HE was higher (HR = 1.88).

During the follow-up, 86 patients developed SBP. The adjusted HR of SBP for current PPI users versus nonusers was 1.72.

It was concluded that PPIs were used by 52% of this international cirrhosis cohort during the one-year period and was a risk factor for developing HE and SBP. The findings were consistent with the hypothesis that PPIs may increase translocation of gut bacteria. These findings suggest that prescription of PPIs in patients with cirrhosis and risk of HE need an appropriate indication.


Mercaptopurine in Treatment of Crohn’s Disease After Surgical Resection

To investigate whether mercaptopurine can prevent or delay postoperative clinical recurrence of Crohn’s disease, a randomized, placebo-controlled, double-blind trial at 29 UK secondary and tertiary hospitals of patients who had a confirmed diagnosis of Crohn’s disease and had undergone intestinal resection was carried out.

Patients were randomly assigned 1:1 by computer-generated, web-based randomization system to oral daily mercaptopurine at a dose of 1 mg/kg body weight rounded to the nearest 25 mg or placebo; patients with low TPMT activity received half the normal dose. Patients and their caregivers and physicians were masked to the treatment allocation. Patients were followed up for 3 years and the primary endpoint was clinical recurrence of Crohn’s disease (CDAI greater than 150 plus 100 point decrease in score), and the need for anti-inflammatory rescue treatment or primary surgical intervention.

Primary and safety analysis were by intention to
treat. Subgroup analyses by smoking status, previous thiopurines, previous Infliximab or methotrexate, previous surgery, duration of disease, or age of diagnosis were also carried out.

Between 06/06/2008 and 04/23/2012, 240 patients with Crohn’s disease were randomly assigned; 128 to mercaptopurine and 112 to placebo. All patients received at least one dose of study drug and no randomly assigned patients were excluded from the analysis.

A total of 16 (13%) of the patients in the mercaptopurine group versus 26 (23%) patients in the placebo group had a clinical recurrence of Crohn’s disease and needed anti-inflammatory rescue treatment or primary surgical intervention (HR 0.54). In a subgroup analysis, 3 (10%) of 29 smokers in the mercaptopurine group and 12 of the 26 in the placebo group had a clinical recurrence that needed treatment (HR 0.13), compared with 13 (13%) of 99 nonsmokers in the mercaptopurine group at 14 (16%) of 86 in the placebo group. The effect of mercaptopurine did not significantly differ from placebo for any of the other planned subgroup analyses.

The incidence of type of adverse effects were similar in the mercaptopurine and placebo groups. One patient on placebo died of ischemic heart disease. Adverse effects caused discontinuation of treatment in 39 of 128 patients in the mercaptopurine and 41 of 112 of the placebo group.

It was interpreted that mercaptopurine was effective in preventing postoperative clinical recurrence of Crohn’s disease, but only in patients who are smokers and Thiopurine treatment seemed to be justified in the preoperative period in those smokers, but smoking cessation should be strongly encouraged.


Oropharyngeal pH Testing for Response to PPI Therapy for Laryngeal Symptoms
To investigate the prognostic potential of oropharyngeal pH monitoring to predict responsiveness to PPI therapy in patients with laryngeal symptoms, the Restech Dx-pH probe was used transnasally to measure oropharyngeal pH. A physician-blind prospective cohort study was conducted at a single academic institution between January 2013 and October 2014 on adult patients with reflux index scores (RSI) 13 degrees or greater off PPI therapy. Patients underwent video laryngoscopy and 24 hour oropharyngeal pH monitoring followed by an 8 to 12 week trial of omeprazole 40 mg daily.

Prior to and following that therapy, patients completed various symptom questionnaires. The primary outcome was the association between PPI response and oropharyngeal pH metrics. PPI response was separated into three subgroups based on the post-treatment RSI score and percentage RSI response. Nonresponse equals RSI 13 or greater; partial response equals post-treatment response less than 13 and change in RSI less than 50%; and complete response equals post-treatment RSI less than 13 and change in RSI greater than 50%.

The primary analysis utilized a multinomial logistic regression controlling for the pre-treatment RSI score. A secondary analysis assessed the relationship between the changes in RSI (post/pre), and oropharyngeal pH metrics by way of ordinary least square regression.

A total of 34 patients completed the study. Symptom response to PPI therapy was as follows: 50% no response, 15% partial response, and 35% complete response. Non-responders had a higher pretreatment RSI. There were no significant differences in oropharyngeal acid exposure (below pH of 4, 5, 5.5, 6, and Ryan scores), between responder types. The secondary analysis showed a trend between lower PPI response and a greater total percent time between pH of 5, upright percentage time below pH of 5, and Ryan supine, as well as association between PPI response and greater decreases in the anxiety sensitivity inventory, brief symptom inventory 18) and negative affect scale.
It was concluded that oropharyngeal pH testing did not predict laryngeal symptom response to PPI therapy, contrary to hypothesis. The degree of oropharyngeal acid exposure is inversely related to PPI response. In addition, reduction in negative effect and psychological distress parallels PPI response.


NSAID Effects in Barrett’s Esophagus

Regular use of NSAIDs is associated with a reduced risk of esophageal adenocarcinoma. To determine whether NSAIDs prevent or decrease the risk of the precursor lesion, Barrett’s esophagus, pooled individual-level participant data from six case-controlled studies of Barrett’s esophagus in the Barrett’s and esophageal adenocarcinoma consortium (BACON), were analyzed.

Medication use was compared from 1474 patients with Barrett’s esophagus separately with two control groups: 2256 population-based controls and 2018 gastroesophageal reflux disease controls (GERD). Study-specific odds ratio (OR) and 95% confidence intervals (CI) were estimated using multivariable logistic regression models and were combined using a random effects meta-analytic model.

As a result, it was identified that regular (at least once weekly) use of any NSAIDs was not associated with the risk of Barrett’s esophagus vs. population-based controls (adjusted OR = 1, 95% CI). Similar null findings were observed among individuals who took aspirin or non-aspirin NSAIDs. We also found no association with highest levels of frequency (at least daily use), and duration (greater than 5 years) of NSAID use. There was evidence of moderate between study heterogeneity; however, association with NSAID use remained non-significant in “Leave One Out” sensitivity analyses.

It was concluded that use of NSAIDs was not associated with the risk of Barrett’s esophagus. The inverse association between NSAID use and esophageal adenocarcinoma may be through reducing the risk of neoplastic progression in patients with Barrett’s esophagus.


Diabetes Mellitus and Relationship to HCC in Cirrhosis

To investigate whether diabetes increases the risk of HCC in patients with cirrhosis and whether the etiology of liver disease modifies the association between diabetes and HCC, all liver cirrhosis patients who had repeated radiographic evaluation of the liver at Mayo Clinic Rochester between January 2006 and December 2011 were included in a study. The Cox Proportional Hazard Regression Analysis was used to investigate the effects of diabetes on the risk of HCC.

A total of 739 patients met the eligibility criteria and 253 had diabetes. After the median follow-up of 38 months, a total of 69 (5%) developed HCC. In patients with HCV infection, diabetes was significantly associated with a risk of developing HCC with an HR of 2.1, whereas in patients with HCV, there was no association (HR 0.8).

When adjusted for covariates, the interaction between HCV and diabetes remained significant (HR for non-HCV = 1.9; HR for HCV = 0.6).

Lack of association between diabetes and HCC was externally validated in 410 patients with HCV cirrhosis enrolled in the HALT-C Trial.

It was concluded that diabetes increases the risk of HCC in patients with non-HCV cirrhosis. In HCV cirrhosis, patients who already have a high risk, diabetes may not increase the risk any further.


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**Oral Contraceptive Use and Ulcerative Colitis Progression**

Oral contraceptive (OC) use has been consistently linked to increased risk of IBD. A specific role of OC in the natural history of ulcerative colitis (UC) requires study and 6104 incident female UC cases aged 16 to 51 years at diagnosis from the Swedish National Patient Register were identified starting in January 2003. Information on current OC use was obtained from the prescribed drug register starting in July 2005. Cases were followed through December of 2014 for primary outcome defined as first UC-related surgery and the secondary outcome was defined by recipient of the first prescription of oral steroids or anti-tumor necrosis factor (anti-TNF) use.

Cox Proportional Hazard modeling was used with time-varying covariates to estimate multivariable Adjusted Hazard Ratio (AHR) and 95% Confidence Interval (CI).

Over 31,421 person/years of followup, 162 cases of UC-related surgery were observed. Compared with nonusers, current and past use of OC were not significantly associated with risk of UC-related surgery (AHR = 0.79 and AHR of 0.74, respectively). The association did not appear to be modified by type of OC use (progestin only, combination of progestin and estrogen), longer duration of use or higher number of dispensed prescription. Similarly, longer use or higher cumulative number of OC prescriptions were not associated with increased risk of receiving a steroid prescription.

In exploratory analyses restricted to Stockholm County, current OC use was not associated with increased risk of receiving anti-TNF therapy (AHR = 0.83).

In a large, nationwide registry of UC patients, it was concluded that there was no association between OC use and UC progression.


**Entecavir and HCC in Chronic Hepatitis B Patients**

To determine whether treatment with Entecavir (ETV) is associated with a reduced HCC risk, study was carried out by calculating the expected HCC incidence based on the risk estimation for HCC and chronic hepatitis B (REACH-B Model), and comparing it with the observed HCC incidence.

The incidence of HCC in the United States patients treated with ETV between 2005 and 2013 in a retrospective cohort was obtained and the predicted HCC incidence was calculated using the above model. The standardized incidence ratios (SIRs) were calculated as a ratio of observed over predicted HCC cases.

Of 841 patients, 646 (65% male, 84% Asian, median age 47 years, 36% HBVe antigen-positive, 9.4% with cirrhosis) met the inclusion criteria. Over a median followup of four years, 17 (2.6%) patients with HCC were diagnosed, including 8 out of 61 patients with cirrhosis and 9 out of 585 (1.5%) without cirrhosis. Compared with those without HCC, the 17 patients with HCC were older at 53 years vs. 47 years and more likely to have cirrhosis at 47.1% vs. 8.4%.

Among patients without cirrhosis, the observed HCC incidence was significantly lower than predicted by the fourth year (SIR 0.137). A sensitivity analysis that comprised all patients, including those with cirrhosis, showed that at the maximum followup time of 8.2 years, a significantly lower than predicted HCC incidence was noted with an SIR of 0.56.

It was concluded that based on the REACH-B model, long-term ETV therapy was associated with a lower than predicted HCC incidence. However, the risk of HCC persisted and careful surveillance remained warranted, despite the antiviral treatment.


**Metabolic Syndrome, Transient Elastography and Prognosis in Chronic Hepatitis B**

To determine whether metabolic syndrome affects the long-term prognosis of chronic hepatitis B (CHB) patients in terms of hepatic events, cardiovascular events, and death, determination of the incidence of hepatic events, cardiovascular events and death in those patients with or without metabolic syndrome were evaluated from 2006 to 2008. A total of 1466 CHB patients were recruited for liver stiffness management (LSM), with transient elastography, together with detailed metabolic profiling as baseline assessment.
Patients were prospectively followed for any clinical events. The impact of LSM and metabolic syndrome on all was evaluated. At baseline visit, the mean age was 46. LSM value was 8.4 and 188 patients (12.8%) had metabolic syndrome.

At a mean followup of 88 months, 93 and 44 patients developed hepatic and cardiovascular events, respectively. A total of 70 patients died. Patients with baseline LSM greater than 8.0 kPa had higher cumulative probability of hepatic events than those with LSM less than 8 at 8 years (12.3% vs. 3.1%).

Patients with metabolic syndrome had higher cumulative probability of cardiovascular events than those without (8.0% vs. 2.0%). High LSM had no impact on cardiovascular events, nor did metabolic syndrome on hepatic events.

LSM greater than 8, but not metabolic syndrome, was an independent risk factor of death, with adjusted hazard ratio of 1.9, respectively.

It was concluded that metabolic syndrome increased the risk of cardiovascular events, with nonhepatic events and death. LSM was the important risk factor of hepatic events and death in CHB patients.


Long-Term Outcome of Endoscopic Resection of Rectal Neuroendocrine Tumors

To determine the long-term clinical outcomes of endoscopically resected rectal neuroendocrine tumors (NETs), according to the pathologic status after initial resection, a large, multicenter, retrospective cohort study was carried out, analyzing the medical records of patients who underwent endoscopic resection of rectal NETs and were followed for greater than 24 months at 16 university hospitals. The outcomes of interest were local or distant recurrence and metachronous lesions.

On the pathologic assessment of 407 patients, the resection margin status was positive at 76 (18.7%), and indeterminate in 72 (17.7% of patients).

Patients whose rectal NETs were diagnosed or suspected as NETs before resection showed a much higher complete resection rate than those whose tumors were resected as polyps and diagnosed.

A total of 14 patients received salvage treatment at 1.9 months +/- 2.8 months after initial treatment during a median followup of 45 months. Local recurrence occurred in three (0.74%) patients, but there was no recurrence of the lymph nodes or distant organs. Metachronous rectal NETs were diagnosed in 3 patients (0.74%).

According to the pathologic status after initial resection, local recurrence of metachronous lesions occurred in one (0.4%) and two (0.8%) patients, respectively in the pathologic tumor-free group, whereas they occurred in two (1.4%) and one (0.7%) patients, respectively in the indeterminate group.

Considering the long-term prognosis, including that for recurrences or metachronous lesions, endoscopic resection is an efficient and safe modality for the treatment of rectal NETs and may result in favorable clinical outcomes in patients with tumors of indeterminate pathology, as well as in pathologic tumor-free cases after initial resection.


HCV Viral Persistence Post Treatment

To assess the presence of HCV RNA in liver explants from 39 patients awaiting liver transplantation who were treated with an interferon-free regimen and had undetectable serum HCV RNA at the time of liver transplantation, 39 patients were evaluated and HCV RNA was detected in most liver explants (67%).

Patients with HCV RNA-positive explants had received shorter courses of treatment and HCV RNA was undetectable in serum for shorter periods before transplantation compared to patients with HCV RNA-negative explants. Levels of HCV RNA in explants were significantly higher in patients with a relapse of HCV infection than patients who responded to treatment, but most patients (85%) with residual HCV RNA in the explant achieved an SVR after receiving their liver transplants.

Improved Diagnostic Criteria for IBS
Symptom-based criteria to diagnose irritable bowel syndrome (IBS) positively performed only modestly. To assess whether including other items from the clinical history and limited diagnostic evaluation improves efficiency of that diagnosis, collection of complete symptoms, colonoscopy and histologic data from 318 consecutive patients, unselected adult patients with lower GI symptoms were carried out in secondary care. All participants underwent colonoscopy, with relevant organic findings recorded. The reference standard use defined the presence of true IBS was patient-reported lower abdominal pain or discomfort associated with a change of bowel habit, in the absence of organic GI disease.

Sensitivity, specificity and positive and negative likelihood ratios (LRs) were calculated for Rome III criteria, as well as for modifications, incorporating nocturnal stools, results of simple blood tests (hemoglobin and CRP), measures of somatization and/or affective disorders (hospital anxiety or depression scale – HADS score).

The sensitivity and specificity of the Rome III criteria for identifying IBS was 69.6% and 82%, respectively, with positive and negative LRs of 3.87 and 0.37, respectively. Clinically useful enhancements in positive LRs were provided by combining Rome III criteria with (a) a high level of somatization – 7.27; (b) normal hemoglobin and CRP with HADS score of greater than 8; (c) normal hemoglobin and CRP with a high level of somatization – 7.56; (d) no nocturnal passage of stool with a high level of somatization – 17.3. Specificity was greater than 95% with each of these modifications.

It was concluded that incorporating nocturnal stools, somatization and affective disorders from the clinical history, as well as hemoglobin and CRP measures, enhances the positive LR and specificity of symptom-based Rome III criteria for IBS.


IBD and Cancer in the Elderly
In the elderly onset IBD patients, the risk of malignancy is of particular concern. In this study on a population-based cohort of elderly onset IBD patients/ French population, 844 patients aged greater than 60 years at diagnosis from 1988 to 2006, including 370 CD and 474 UC was carried out, comparing the incidence of cancer among IBD patients with that observed in the French network of population-based cancer registries (FRANCIM).

Results were expressed using the standardized incidence rates (SIRs) and their confidence interval (CI 95%).

Median age at IB diagnosis was 70 in CD and 69 in UC. Median followup was 6 years for both, with the number of person/years of 5598. Among the 844 elderly onset IBD patients, 98 (11.6%), 42 CD and 56 UC developed the cancer after IBD diagnosis (67 men and 37 women), corresponding to an overall SIR of 0.97. These cancers occurred at a median age of 77 years and 75 years in patients with CD and UC, respectively. Median time between IB diagnosis and cancer was 78 months (40 to 121). There was no increased risk of colorectal cancer in IBD (SIR = 1.03, CD SIR = 1.20), nor in UC (SIR = 0.91), without significant protection of 5ASA (HR = 0.7).

No significant risk for other intestinal cancers was found, especially for small bowel carcinoma. An increased risk of malignant lymphoproliferative disorders was found in all IBD and in CD (SIR = 2.49 and SIR = 3.09, respectively). An increased risk of myeloproliferative disorders was found in all IBD (SIR = 2.18). Thiopurine exposure using a time-dependent Cox model was not found as associated with increased risk to develop cancer (HR = 0.90).

It was concluded that there is no increased risk for developing intestinal cancer among patients with elderly onset IBD in this population-based cohort. There are increased risks of developing lymphoproliferative and myeloproliferative disorders in all IBD. Thiopurine exposure was not found to be associated with that risk. This data reinforced the difference between elderly onset IBD compared with patients with younger age at IBD onset.


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