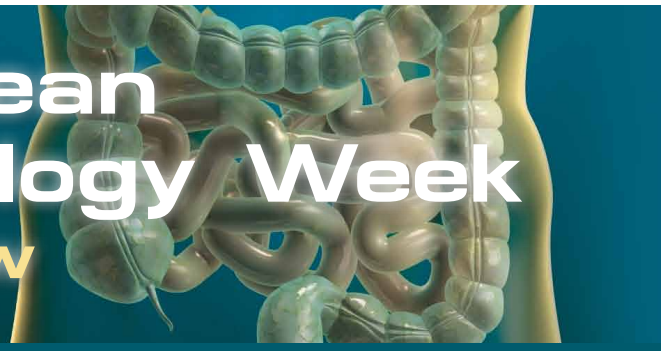
United European Gastroenterology Week
Conference Review



Making Education Easy

22 – 26 October 2011, Stockholm, Sweden

In this review:

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Welcome to our review of the 19th United European Gastroenterology Week (UEGW) held in Stockholm, Sweden on 22–26 October 2011.

The review is a summary of some of the latest and most exciting developments in gastroenterology presented at the meeting. Drs Jim Brooker and Alan Fraser attended UEGW 2011 and have selected and reviewed the presentations that they felt were most significant and relevant to local practice.

I hope you find this conference review stimulating, and I look forward to your feedback.

Kind regards

Chris Tofield

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Evaluation of montelukast efficacy in maintaining both clinical and histopathological remission achieved by using topical corticosteroids in adult eosinophilic esophagitis patients

Authors: Lucendo Villarin A et al

Summary: In a prospective study in patients with eosinophilic esophagitis (EoE), Spanish investigators examined the effect of the leukotriene inhibitor montelukast in the maintenance of topical steroid induced remission. In 9 male and 2 female patients (mean age 34.9 years) who had experienced oesophageal symptoms of EoE for an average of 42.6 months (range 12-72 months) and who had received fluticasone propionate 400 µg twice daily for 6 months, montelukast 10 mg/day was initiated as replacement therapy for 3 months. Eosinophilic density into the epithelium and lamina propria (as assessed by oesophageal biopsies) decreased after topical corticosteroid therapy and increased after montelukast therapy, but did not return to pretreatment levels. In four patients serious deterioration in symptoms in the second month of treatment prompted cessation of montelukast therapy.

Comment (JB): Previous small case series have suggested a potential role for the leukotriene receptor antagonist montelukast in EoE. In this prospective study from Spain, 11 patients with EoE showed a significant improvement in dysphagia score and tissue eosinophilia after 6 months of fluticasone therapy (400 µg bid). Fluticasone was then replaced with montelukast 10 mg/day for 3 months. Symptom scores and tissue eosinophil levels both significantly deteriorated, though not returning to baseline. Four patients withdrew because of significant deterioration of dysphagia.

The evidence for montelukast in this condition is weak and conflicting, and does not support its routine use. A randomised controlled trial is needed to lay this question to rest once and for all. There is better data supporting topical corticosteroids, dietary manipulation (the "six food elimination diet") and even for cautious oesophageal dilatation for EoE, with an excellent overview presented at the meeting by Dr Alex Straumann of Switzerland.

Poster presentation: # P0769

Reference: Gut 2011;60(Suppl 3):A263

26-week efficacy and safety of once-daily oral linaclotide in patients with irritable bowel syndrome with constipation: a European perspective

Authors: Lembo A et al

Summary: To evaluate the efficacy and safety of linaclotide for the treatment of irritable bowel syndrome with constipation (IBS-C; modified Rome II criteria), 804 patients (female 90%; median age 44 years) were treated with linaclotide 266 µg/day (n = 401) or placebo (n = 403) for 26 weeks. A response in one co-primary parameter (≥30% reduction in abdominal pain or discomfort with neither score worsening for ≥6 of the first 12 weeks) was observed in 54.1% of linaclotide and 38.5% of placebo recipients ($p < 0.0001$). In a second co-primary parameter ('considerably relieved' or 'completely relieved' on the degree-of-relief of IBS symptoms question for ≥6 of the first 12 weeks) the response rates were 39.4% and 16.6% ($p < 0.0001$). These response rates were maintained at 26 weeks (53.6% vs 36%, 37.2% vs 16.9%; both $p < 0.0001$). Over the first 12 weeks, linaclotide also improved complete spontaneous bowel movements, stool consistency, straining, bloating, spontaneous bowel movements, abdominal pain and discomfort versus placebo ($p < 0.0001$).

Comment (JB): Linaclotide is a 14-amino acid peptide antagonist of the guanylate cyclase-C receptor, acting via cGMP to open anion channels, increase secretion, speed transit and, it is also believed to reduce visceral hypersensitivity. Administration is once daily, with minimal systemic absorption. This paper reports a phase III, multicentre double-blind, randomised controlled trial in 804 patients with severe IBS-C, showing modest, significant improvements in all symptom groups compared with placebo, sustained for 26 weeks of therapy. The commonest side effect was diarrhoea, leading to discontinuation in 4%. This is the most promising new drug for IBS-C and chronic constipation since the 5HT4 agonist Tegaserod was withdrawn in 2007. Linaclotide is not yet licensed but the data is scheduled for FDA review in 2012, and the European marketing company Almirall was promoting it heavily in Stockholm.

Oral presentation: #OP174

Reference: Gut 2011;60(Suppl 3):A41

Efficacy and safety of tacrolimus therapy in steroid-refractory or steroid-dependent active moderate to severe ulcerative colitis: a single-centre retrospective French experience

Authors: Boschetti G et al

Summary: To determine the safety and efficacy of long-term tacrolimus therapy for moderate to severe ulcerative colitis (UC) in patients who are steroid refractory or steroid dependent, a French team retrospectively assessed the records of 20 adult (mean age 37.2 years) patients. The median period of tacrolimus treatment was 2.5 months at a dosage of 0.1–0.15 mg/kg body weight/day given in twice daily divided doses; serum trough target levels of 10–15 ng/mL. Tacrolimus was started a median of 5 years after disease onset in patients with moderate (n = 7) and severe (n = 13) active disease. Eight (40%) patients achieved remission according to the partial Mayo score, while a clinical improvement was observed in five (25%) patients. A total of 14 patients (70%) remained colectomy-free during the follow-up period (median duration 14.5 months), with a mean time to colectomy of 12.8 months.

Comment (JB): This poster describes the retrospective experience of a single French centre with the oral calcineurin inhibitor tacrolimus, in 20 adult patients with moderate to severe, steroid-refractory (n = 17) or -dependent (n= 3) UC. Disease was extensive in 70% and left sided or rectal in the remainder. Target trough levels took just over a week to achieve with oral weight-based therapy as reported elsewhere previously. Oddly only two patients received concomitant immunomodulatory therapy (methotrexate), and prior azathioprine therapy was not mentioned. 65% of patients responded (remission 40%, improvement 25%), with 70% remaining colectomy free. Adverse effects led to discontinuation in 4 patients, the most common being tremor and hypomagnesemia.

The therapeutic options are limited in those intolerant or refractory to conventional treatments. This study adds to the slowly building data supporting moderate efficacy and reasonable toxicity profile of tacrolimus in the short to medium term. Prospective studies are needed to assess long-term efficacy and safety. This remains an unlicensed, unfunded treatment.

Poster presentation: #P0921

Reference: Gut 2011;60(Suppl 3):A296

A novel biomarker assay to predict progression of Barrett's esophagus: results from the long term prospective follow up studies

Authors: Pacha A et al

Summary: In order to evaluate the utility of a novel biomarker assay of the tumor suppressor genes p16 and p53, and aneuploidy status (using two chromosome probes, 7 and 17) a Dutch group analysed fluorescence in situ hybridisation (FISH) on brush cytology specimens from a study cohort of 135 patients with Barrett's oesophagus in a 5-year follow-up study. Initially 95% of patients had gradings of no dysplasia or indefinite for dysplasia (ND/IND) while 5% had low-grade dysplasia (LGD); 14 cases progressed from (ND/IND) to either LGD or high-grade dysplasia (HGD), and 2 progressed from LGD to HGD. Positive FISH markers were detected in 14 of the 16 who progressed, but in only 28 of those who did not progress (p = 0.001). A Cox regression model indicated a HR of 5.5 (p = 0.002) in those with a positive marker. In a validation cohort, histological progression was seen in 8.5% patients and all tested positive for the marker versus 20% of those who did not progress (p = 0.001)

Comment (JB): A number of characteristics have been helpful in identifying those at higher risk of progression of Barrett's oesophagus, including Barrett's length, ulceration, gender, BMI and ethnicity. The Amsterdam group has looked in a blinded study at novel cytologic biomarkers (loss of P16 or p53 expression, or the detection of aneuploidy) by fluorescence in situ hybridisation (FISH). Follow-up is complete (5 years) in 301 of 451 patients enrolled in two separate series (a study cohort and a multicentre validation cohort). The baseline distribution of the biomarkers was similar between the two groups. Abnormalities of any of the markers predicted a higher risk of progressing from non-dysplastic, indeterminate histology or low-grade dysplasia to a more advanced lesion, with a hazard ratio of 5.1 to 9. From the Kaplan Meier curves displayed at the presentation the negative predictive value would appear to be above 95%. If these data are reproducible this technology may allow resources to be targeted at patients who need closer surveillance.

Oral presentation: #OP050E

Reference: Gut 2011;60(Suppl 3):A12

Treatment outcome of achalasia depends on the manometric subtype

Authors: Rohof W et al

Summary: To determine whether achalasia treatment efficacy in an earlier study was dependent on manometric subtype, a European group compared manometric tracings from 176 of 201 patients randomised to pneumatic dilation (PD) or laparoscopic Heller myotomy (LHM). Type 1 achalasia (no pressure waves in the distal esophagus [amplitude <30 mmHg]) occurred in 44 patients (25%), type 2 (panesophageal pressurisation [>30 mmHg]) in 114 patients (65%) and type 3 (rapidly propagating contraction attributable to spastic contraction [>70 mmHg, duration of >6 s]) in 18 patients (10%). Success rates after 2 years were significantly higher in type 2 patients (96%) versus type 1 (81%; $p < 0.01$) or type 3 (66%; $p < 0.001$) patients. In a Cox regression analysis, type 1 (HR 4.0; 95% CI 1.5–11) and type 3 (HR 6.8; 95% CI 2.3–20) are highly predictive of treatment failure compared to type 2. PD treatment success (allowing redilation in 7 patients) was higher than LHM success rates (100% vs 95%; $p = 0.03$) in type 2 achalasia, but not in type 1 (85% vs 81%) or type 3 (40% vs 86% [n = 18]) achalasia.

Comment (JB): The role of surgical versus endoscopic therapy in achalasia has recently been clarified in a large prospective multicentre European study. The two approaches were shown to have very similar outcomes. The same group has now performed a subanalysis to determine the relative outcomes according to the type of achalasia. The most favourable response to intervention was observed in the commonest group (65%) type 2, with efficacy of 100% for pneumatic dilatation (PD), significantly greater than the 95% for myotomy (HM). Type 1 responded a little worse, but both modalities were equal. On the other hand there was a trend in type 3 for poorer response to PD (40%) than HM (86%), with this group probably too small to achieve significance. Classification of achalasia appears to be useful in predicting outcome of therapy and may assist in choosing the modality.

Oral presentation: #OP332

Reference: Gut 2011;60(Suppl 3):A76

Independent commentary by Drs Alan Fraser andJim Brooker.

Dr Alan Fraser is Associate Professor of Medicine at the University of Auckland. He consults at Auckland Gastroenterology, Mercy Specialist Centre. His research interests are Helicobacter pylori infection, inflammatory bowel disease and the audit process for endoscopic procedures. He has published over 100 research papers. He is secretary for the New Zealand Society of Gastroenterology and chair of the SAC committee that overseas training in gastroenterology in New Zealand.

Dr Jim Brooker is a Consultant Gastroenterologist at Waikato Hospital, Hamilton. His interests include luminal gastroenterology and new endoscopic technology; capsule endoscopy, balloon enteroscopy and radiofrequency ablation for Barrett's. He also has an interest in oesophageal manometry and impedance pH testing.

Radiofrequency ablation of Barrett's esophagus with high-grade dysplasia or early cancer: durability of treatment response at 5-year follow-up visit

Authors: Phoa KYN et al

Summary: To assess the long-term durability of radiofrequency ablation (RFA) with or without prior endoscopic resection (ER) for eradication of Barrett's oesophagus (BE) containing dysplasia, Dutch investigators provided 5-year follow-up data on a prospective cohort of 23 BE patients who achieved complete epithelial reversion 1 year after RFA +/- ER. Sustained complete histological remission of high-grade dysplasia or early cancer and of intestinal metaplasia was observed (using endoscopy with narrow-band imaging) in all patients at 5-year follow-up. No buried Barrett glands were observed in neosquamous epithelium biopsies.

Comment (JB): The Amsterdam group has now reported its 5-year follow-up for combined RFA +/- ER in a small cohort of 23 patients with high-grade dysplasia or early carcinoma in Barrett's oesophagus. Four patients exited the study for unrelated reasons. With 100% complete remission of intestinal metaplasia and early cancer, and no buried glands, these results provide reassurance that the impressive early results of RFA +/-resection are sustained. The need for occasional rescue endoscopic resection of visible neoplastic lesions that may arise during the course of therapy is a warning to be vigilant. The significance of occasional IM at the cardia is unknown at the moment.

Oral presentation: #OP023

Reference: Gut 2011;60(Suppl 3):A5

E-health: the impact of web-based (traffic light) monitoring of disease activity and timing of infliximab treatment on the inflammatory burden

Authors: Pedersen N

Summary: Danish investigators performed an open label pilot study in 23 patients (12 females; median age 38 years) to determine the efficacy and safety of a web-based program developed to optimise maintenance treatment with infliximab (IFX) and the control of inflammation in patients with Crohn's disease (CD) over 52 weeks. Overall, 120 infliximab infusions were delivered with a median interval of 9 weeks. The mean interval between infliximab infusions was <8 weeks (<Q8) in 3%, 8 weeks (Q8) in 26% and >8 weeks (>Q8) in 61% of patients. Twelve patients also received concomitant immunosuppressive therapy with azathioprine/6-mercaptopurine (n = 9) or methotrexate (n = 3). No significant difference was observed in inflammatory burden between baseline and end of follow-up (3 vs 4; $p = 0.09$), nor amongst the <Q8, Q8 and >Q8 groups at baseline (5 vs 3 vs 2) or at the end of follow-up (4 vs 6 vs 4).

Comment (AF): This Danish group have been exploring ways of using the internet to enhance the quality of health delivery as well as options to save money. This study relied on the patient submitting regular samples for faecal calprotectin assays - the results were automatically logged onto the website and information regarding the appropriate interval for the next infusion sent to the patient. Some money could be saved for the same endpoint (minimal inflammatory activity), but the mean interval between infusions was only extended to 9 weeks compared to the usual protocol of 8-weekly infusions.

Poster presentation: #PO421

Reference: Gut 2011;60(Suppl 3):A191

Post-diagnosis aspirin usage in colorectal cancer is associated with improved all-cause and disease-specific mortality

Authors: Steele R et al

Summary: To determine whether the use of aspirin is associated with improved outcomes for patients diagnosed with colorectal cancer, a Scottish group analysed cancer registry data from 1997-2006, prescription records from 1993–2010 and death records to 2010. In total, 2990 colorectal cancer patients were identified with a median age at diagnosis of 73 years. During follow up 1998 (67%) deaths were recorded with 1021 (34%) attributed to colorectal cancer. Cox proportional hazard models indicated that aspirin use after diagnosis was associated with a reduced mortality risk (HR = 0.67; 95% CI 0.57–0.79, $p < 0.001$) and a lower risk of death from colorectal cancer (HR = 0.54; 95% CI 0.48–0.60; $p < 0.001$) after controlling for age, Dukes' stage, gender, socioeconomic status and pre-diagnosis aspirin use. Increased mortality and colorectal cancer death risk were associated with increasing age and Dukes' stage, while the top two socioeconomic quintiles were at reduced risk. They concluded that use of aspirin after diagnosis of colorectal cancer is associated with a reduced risk of both all cause and colorectal cancer specific mortality.

Comment (AF): This study shows the power of a long-term all-cause mortality study. It is well established that the humble aspirin can prevent CRC (perhaps by 50%), but it is surprising and encouraging that aspirin can reduce all-cause mortality after the diagnosis of CRC by 33% and CRC-related mortality by close to 50%. The study showed that increasing age and more advanced CRC increased the risk of a cancer death and that higher socioeconomic status decreased the risk (as has been shown for other malignancies). The widespread use of aspirin has not been advocated as a public health policy to prevent CRC, but targeted treatment after the diagnosis of CRC is a real option.

Oral presentation: #OP279

Reference: Gut 2011;60(Suppl 3):A64

Colorectal neoplasia in patients with primary sclerosing cholangitis undergoing liver transplantation: a Nordic multicenter study

Authors: Jorgensen KK et al

Summary: To assess the risk of colorectal neoplasia in patients with primary sclerosing cholangitis (PSC) with inflammatory bowel disease (IBD) undergoing liver transplantation, a multicentre Nordic team assessed 439 patients with PSC. In total, 353 patients (80%) had IBD at the time of transplant, and 15 (3%) more developed IBD after transplant. The median duration of IBD was 15 years at the time of transplant and the median follow-up period was 5 years. Colorectal neoplasia developed in 91 (25%) patients during follow-up and the overall cumulative risk was 6.5% after 10 years and 17% after 20 years from diagnosis of IBD. Cumulative colorectal neoplasia risk was higher after transplantation (HR 1.9; 95% CI 1.3–2.9; p = 0.002). Multivariate analysis indicated that aminosalicylates, ursodeoxycholic acid and tacrolimus, but not IBD duration or activity, anti-rejection treatment or cytomegalovirus infection were risk factors for colorectal neoplasia after liver transplant.

Comment (AF): This large study of PSC and colorectal cancer (CRC) gives further strong evidence of the significantly increased risk of CRC in PSC (83% developed IBD). Importantly, there is an additional increase in risk after transplantation. The multivariate analysis throws up some surprising factors that may have increased risk, but these findings will need to be confirmed in other studies. 5-ASA medications clearly reduce the risk of CRC in IBD when considering all cases.

Oral presentation: #OP002

Reference: Gut 2011;60(Suppl 3):A1

Biologic use is associated with a major reduction in venous thromboembolic events compared with steroid use in the treatment of inflammatory bowel disease

Authors: Higgins P et al

Summary: In order to determine whether biologic therapies for the treatment of active IBD would decrease the risk of venous thromboembolic events (VTE) compared to corticosteroids, a US group performed a retrospective analysis of data from 15 100 adult subjects in the MarketScan database with ≥1 inpatient diagnosis or ≥2 separate outpatient codings of CD or UC. In total, 325 VTEs occurred during the analysis period (Jan 2003–Dec 2009). For the steroid without biologic, biologic without corticosteroid, and combination biologic plus corticosteroid groups the VTEs rates were 2.3%, 0.4% and 2.5%, respectively. When compared to corticosteroids without biologics, patients on biologics had an odds ratio (OR) of 0.21 (95% CI 0.05–0.84) for VTEs in a multivariate model. Subjects receiving both corticosteroids and biologics had an OR of 0.99. Significant covariates included age (OR 1.02 per year of age), recent IBD surgery (OR 3.62), recent IBD hospitalisation (OR 1.51), cancer (OR 2.33) and indeterminate colitis (OR 1.61). Corticosteroid use was associated with a nearly 5-fold increase in VTE risk over that of biologic therapy.

Comment (AF): The risk of VTE with IBD is significant. This partly relates to disease activity. Biologicals are able to switch off the procoagulant effect of IBD, whereas corticosteroids are actually a significant risk factor for VTE. The other co-variates identified are well established as risk factors for VTE in the absence of IBD.

Oral presentation: #OP143

Gut 2011;60(Suppl 3):A34

Predictive factors of disease relapse following thiopurine withdrawal for sustained clinical remission in IBD

Authors: Gambles CJ et al

Summary: In order to determine the relapse rate of patients with UC or CD following azathioprine (AZA) or mercaptopurine (MP) withdrawal, researchers from Great Britain conducted a retrospective analysis of an IBD research database in Edinburgh. A total of 1836 electronic case notes were examined (971 for UC and 865 for CD) of which 633 patients were treated with a thiopurine (286 for UC and 347 for CD). Of these, 76 patients (30 UC and 46 CD) met the strict inclusion criteria for the study (i. AZA and/or MP therapy for ≥3 years; ii. AZA/MP withdrawn because of sustained clinical remission [defined by global physician assessment at withdrawal]; iii. no steroid therapy for 6 months prior to withdrawal; iv. minimum 12-month follow-up). The relapse rates at 12 and 24 months were 13.3% and 26.7% for UC and 46% and 59% for CD. Univariate analysis indicated a platelet count of ≥300x10^9/L was associated with a greater risk of relapse for UC. Inflammatory disease behaviour (Montreal B1 vs B2+B3) was significantly protective against relapse in CD (p = 0.007).

Comment (AF): This study shows that retrospective case reviews still have a place in clinical research. The study aims to look at the relapse rate after sustained remission (at least 3 years). The rates for UC are lower than expected (based on data for all patients stopping thiopurines for a variety of reasons). This illustrates that the "depth" of remission is important for predicting outcome after stopping medication. The much higher rates of relapse for CD show what a difficult disease this is - stopping thiopurines has a significant risk. The predictive value of the platelet count illustrates how useful this test is in monitoring IBD. Perhaps a platelet count at the upper end of the normal range suggests some residual inflammatory activity. It is of little surprise that CD with previous stricture or perforation (B2,B3) behaves more aggressively after stopping thiopurines.

Oral presentation: #OP271

Reference: Gut 2011;60 (Suppl 3):A62

Assessing the risk of irritable bowel syndrome following acute gastroenteritis in The Netherlands

Authors: Kowalcyk BB et al

Summary: This Dutch study aimed to estimate the relative risk of IBS one year after acute gastroenteritis (GE) and explore potential risk factors for IBS using data from the Primary Care Network Utrecht (PCNU) database (a prospective cohort with routine consultation data from ≥60 000 patients) 1998–2009. A total of 2 839 patients aged 18 to 70 met a strict case definition of GE and had no history of cancer, alcohol abuse, GE symptoms in the previous 12 months, pre-existing IBS/IBD or abdominal surgery, or ≥5 prescriptions for IBS or IBD treatment. At one year, 8.2% of GE patients had been diagnosed with IBS compared with 1.1% in a comparison cohort (without IBS and matched by age, sex, consulting practice and time of visit) of 2 711patients. Patients who had experienced GE had an increased risk of IBS (RR 7.3; 95% CI 5.0–10.6).

Comment (AF): IBS after acute gastroenteritis is a significant public health problem leading to many days off work and loss of quality of life. This well conducted study reinforces the extent of the problem. The relative risk of developing IBS after gastroenteritis was 7.3. Risk factors for IBS after acute gastroenteritis were female gender, cramps or blood during the illness (presumably more severe gastroenteritis has a higher risk) and previous consulting practice.

Poster presentation: #P1004

Reference: Gut 2011;60(Suppl 3):A314

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