A special series of reports from

DIGESTIVE DISEASE WEEK 2008

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Digestive Disease Week (DDW) is considered the largest and most prestigious meeting in the world for the gastrointestinal professional. Each year DDW features leading researchers and clinicians in the field of gastrointestinal medicine discussing the latest research in gastroenterology, hepatology, endoscopy and gastrointestinal surgery. The following report is based on a selection of key sessions with commentary by leading Australian specialists.

Emerging Therapies for IBS

Report by Dr Martin Weltman
Associate Professor of Medicine University of Sydney; Head of The Department of Gastroenterology and Hepatology Nepean Hospital. Special interests include hepatology and inflammatory bowel disease.

Therapy for irritable bowel syndrome has been limited. Dr William Shey reviewed both current treatment approaches and clinical trials for diarrhoea and constipation predominant IBS. Therapies for constipation predominant IBS appear to be more evolved and clinicians will need to have an understanding of these drugs as they (likely) become available over the next few years.

IBS with diarrhoea

The main therapeutic agent still in (restricted) use in the USA (not available in Australia) is Alosteron. The latter is only effective in women with severe diarrhoea predominant IBS. These patients usually have associated abdominal pain and as a group have been documented to have reduced quality of life scores. While this drug has been largely successful in this group of patients, 30 % of patients develop constipation. Ischaemic colitis has also been reported. Unfortunately the latter has been associated with a significant number of hospitalisations and even deaths. It is unlikely that this drug will become available in Australia.

Other agents that are currently undergoing clinical trials include drugs which reduce chlorine secretion such as: crofelemer, a novel proanthocyanidin; R-Verapamil, a calcium channel blocker: and asimadoline, a Kappa-opioid antagonist.

The outcomes of these studies are keenly awaited as diarrhoea predominant IBS is a common clinical problem.

IBS with constipation

Tegaserod provided some potential for therapeutic intervention, but was withdrawn from the market because of significant CVS complications.

Chloride channel stimulants, such as Lubiprostone (Amitiza) have now become available in the USA. Lubiprostone appears to be well tolerated by this patient group including elderly patients and is currently being evaluated for the use in post-operative bowel dysfunction and in opioid induced constipation. The drug works by stimulating chloride channels on the apical aspect of gastrointestinal epithelial cells to produce a chlorine rich secretion. In turn, this secretion softens stools, promotes an increase in bowel motility and consequently enhances stool production. Side effects include nausea, diarrhoea, headaches, abdominal pain and abdominal distension, but overall only 1% of patients experienced side effects.

Renzapride is another drug in development and is both a partial 5HT3 antagonist and a full 5HT4 agonist. We need to wait for the outcomes of clinical trials to be published.

MD-1100 acetate (Linaclotide) is currently undergoing clinical trials in constipation predominant IBS. It is an orally delivered compound that has been shown in preclinical testing to promote gastrointestinal transit and secretion and also to alleviate gastrointestinal pain. It appears to specifically target the gastrointestinal tract. The drug works by acting on guanylate cyclase-C, a receptor found on the surface of intestinal cells. Phase 2 studies reveal that patients experience an increase in stool frequency and an improvement in stool consistency.

Subcutaneous Methylnaltrexone (Relistor), a mu-opioid-receptor antagonist, which has restricted ability to cross the blood-brain barrier, has been investigated for the use of management of opioid induced constipation. It appears to provide a significant laxative effect. Treatment did not appear to affect central analgesia or precipitate opioid withdrawal. This drug is currently being evaluated for constipation-predominant IBS and post-operative ileus. Relistor is approved for use in Europe and Canada.

Abstracts contributing to this report:
Lubiprostone Significantly Improves Symptom Relief Rates in Adults with Irritable Bowel Syndrome and Constipation
Effects of Novel, First-in-Class Guanylate Cyclase-C Activator, Linaclotide Acetate (MD-1100), on Gastrointestinal and Colonic Transit and Bowel Habits in Patients with Constipation-Predominant Irritable Bowel Syndrome.

Radiofrequency Ablation (RFA) of Barrett's Oesophagus with Dysplasia : The balloon is back.

Report by Dr Luke Hourigan
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The future utility of RFA in Barrett's Oesophagus depends on its ability to ablate dysplasia, particularly high grade dysplasia (HGD). DDW 2008 saw the release of the interim results of some of the major studies assessing this treatment modality.

Nicholas Shaheen presented the interim results of the *Ablation of Intestinal Metaplasia (AIM) dysplasia trial : A randomized, multicenter, sham controlled trial of RFA for dysplastic Barrett's Oesophagus* at the SSAT Presidential Plenary. Subjects were randomized to RFA or sham (2:1) and stratified by dysplasia grade and segment length (<4 vs 4-8cm). Stepwise circumferential and focal ablation was performed using the HALO system (max 4 sessions). Of 127 pts, 58 (46%) reached the primary endpoint (complete histological clearance of IM, LGD or HGD at 12 months). 74% of RFA subjects achieved complete clearance of IM compared to 0% sham, and 85% were free of dysplasia. There were no perforations and one stricture which was managed with a single dilatation.

Preliminary data from the first European Multicenter trial (Pouw *et al*) evaluated the safety and efficacy of RFA with or without prior endoscopic resection (ER). Twenty four patients were treated, with 22 patients undergoing a total of 24 ER sessions (16 mucosal adenocarcinoma and 6 HGD) and 2 patients underwent RFA only. The worst residual histologies found prior to RFA were: 11 patients with HGD, 9 patients with LGD and 4 patients with IM. Complete eradication of all dysplasia and IM was achieved in 23 patients (96%) after a single *HALO 360* (circumferential ablation) treatment and a mean of 1.5 *HALO 90* (focal ablation) treatment sessions (additional ER were required in 2 patients). Complications of the procedure included: 4 with minor mucosal injury, 1 patient with melaena and 1 patient developed a stricture requiring dilatation. Data so far suggests that stepwise circumferential and focal RFA of Barrett's Oesophagus with early neoplasia (with or without ER) is highly effective for the complete eradication of Barrett's oesophagus and associated dysplasia without serious adverse events.

Other studies concluded that RFA preserves oesophageal motility, lumen size and compliance (Hanneke *et al*). RFA has so far been associated with significantly fewer strictures compared to Photodynamic Therapy (Bumgarner *et al*).

The preliminary data presented suggests some early promising results for the use of RFA in the management Barrett's high grade dysplasia. Combination of ER and subsequent RFA (to avoid metachronous lesions) may represent the shift of the pendulum towards endoscopic management for early oesophageal malignancy. It is clear that there will a requirement for rigorous endoscopic surveillance in both settings.

The *HALO* device is presently approved for use in Australia. It is my opinion that this device should presently be used strictly in the tertiary hospital research setting.

Third Eye Retroscope Offers Complementary View

Report by Dr Martin Weltman
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For the first time at this year's, DDW, the Avantis 'Third Eye' retroscope system was demonstrated. This is a new device to assist with colonoscopy surveillance for polyps and colorectal cancers. This is a disposable device that provides an additional view to reveal polyps, cancers and other lesions that might be hidden from the lens of the traditional forward-viewing colonoscope.

The device is passed through the instrument channel of a standard colonoscope until it extends beyond its tip. As it emerges, the device automatically turns around 180 degrees to aim "backward" toward the tip of the colonoscope. Then, as the colonoscope is withdrawn from the colon, the Third Eye comes along with it, providing a continuous retrograde view to complement the forward view of the colonoscope.

Previous studies have revealed that up to12-24% of polyps and a significant number of cancers can be missed during colonoscopy, especially if they lie behind folds in the colon wall. This new device is designed to solve that problem by allowing the physician to view the opposite side of those folds during the procedure.

A study using an anatomical model revealed that of the polyps located on the proximal aspect of haustral folds in the models – i.e., the opposite side when viewed from below – the endoscopists detected only 12% with a standard colonoscope. However, they found 81% of the polyps when using a prototype of the Third Eye Retroscope in conjunction with an identical colonoscope.

Data from a muli-centre study was presented by Jerome Waye at DDW 2008. The study, which is still active, has found that, in combination with a standard colonoscope, the Third Eye Retroscope detected 13.3% additional polyps, and 12.4% additional adenomas, compared with the colonoscope alone. Polyps detected with the Third Eye were comparable in size to those seen with the colonoscope.

Waye JD, Heigh RI, Fleischer DE, et al. A prospective efficacy evaluation of the third eye retroscope auxilliary endoscopy system. Gastrointest Endosc 2008; 67: AB101-2.