Therapeutic Advances in Gastroenterology

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What are the therapeutic advances in gastroenterology? Opinions from world experts

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Introduction

This year's Digestive Diseases Week (DDW), held recently in San Diego, USA, showed us how far we have come in treating gastrointestinal and hepatic diseases. The conference was a vital exposition of our successes, our current thinking, latest results and future steps. It explored the areas of basic science where there is intense activity into the causes and mechanisms of disease, and also revealed the clinical advances we are making with new drugs, regimens and strategies. This type of conference will be repeated across several continents this year, and collectively they will lead to the dissemination of best evidence and clinical practice in gastrointestinal (GI) medicine. This is also the focus of *Therapeutic Advances in Gastroenterology*, aided and abetted by our international editorial board. Thus, we thought it would be timely to ask for their opinions on significant therapeutic advances in gastroenterology, what the future holds, and what needs to be addressed. This collation of expert comment provides a clinical picture of where we are currently, and where we need to head in the years to come. Whether or not the following views are shared or disparate does not matter – the point is that research in gastroenterology is in good hands and will continue to thrive in the years to come.

Upper gastrointestinal tract and Barrett's esophagus

Doug Taupin (*The Canberra Hospital, Canberra, ACT, Australia*) singles out the development of long-acting potent antisecretory agents as a major step forward. Agents that reliably reduce

24-h esophageal acid exposure may be useful in preventing Barrett's esophagus developing into dysplasia, he says [Romero, 2006].

Julian Abrams (*Columbia University College of Surgeons, New York, NY, USA*) comments on the one-year results of the AIM Dysplasia trial, reported at this year's DDW [Shaheen *et al.* 2008]. In short, radiofrequency ablation for high-grade dysplasia in Barrett's esophagus was shown to be 80–90% effective and associated with only a 5% stricture rate. He believes it will be important to see how durable its effect is, and is looking forward with interest to see the results of the upcoming trial of ablation using cryotherapy with liquid nitrogen. As far as current issues that need to be resolved, he states that we need to know if there are effective chemotherapeutic interventions available. The results of the AsPECT trial examining the role of aspirin and proton pump inhibitors in the prevention of progression in Barrett's esophagus are eagerly awaited [Jankowski and Moayeddi, 2004]. He believes the next step will be to identify which subpopulation of Barrett's patients is at highest risk for progression to cancer. In this manner, preventive measures can be targeted and have the highest impact.

Eradicating *Helicobacter pylori* infection for treatment of gastritis, peptic ulcer, and gastric MALT lymphoma, and prevention of gastric cancer has been a major advance according to Jaw-Town Lin (*National Taiwan University Hospital, Taipei, Taiwan*). In oriental countries, more than 50% of the total population had been infected

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with *H. pylori*, and many had peptic ulcer or gastric cancer, commented Tsutomu Chiba (*Kyoto University, Kyoto, Japan*). With *H. pylori* eradication, the number of those patients, particularly peptic ulcer patients, has been decreased significantly in recent years. Ben Wong (*University of Hong Kong, Hong Kong*) summarized recent important guidelines and reviews on this topic [Cheung and Wong, 2008, Fock *et al.* 2008, De Vries and Kuipers, 2007, Fuccio *et al.* 2007, Sugano, 2007]. Most reports support the early treatment of *H. pylori* infection as a preventive measure for stomach cancer, and he believes the next challenge in stomach cancer and *H. pylori* infection will be that of treatment-related risks and antibiotic resistance, and also if countries should adopt nationwide screening and eradication of *H. pylori* as a public health measure. Deng-Chyang Wu (*Kaohsiung Medical University Hospital, Hong Kong*) looks forward to the convenience of a single capsule that includes triple or quadruple therapy.

Jaw-Town Lin commends the advances in cancer treatment, in particular for upper GI cancers, such as targeted therapy (e.g., imatinib therapy for GI stromal tumor [GIST]); endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for Barrett's esophagus; and treatment of superficial cancers of the esophagus (as well as stomach and colon). Tsutomu Chiba comments that, in Japan, 95% of his esophageal cancer patients have squamous cell carcinoma, and many of them are successfully treated by EMR. Doug Taupin, however, has asked if EMR and submucosal resection for localized cancers are a genuine advance or not. He also states that a reliable percutaneous endoscopic gastrojejunostomy is still required. The success rate of achieving jejunal placement is poor and the tubes clog and migrate proximally, he comments. Even the best centers have 20% complication rates leading to tube removal or replacement.

Deng-Chyang Wu highlights the development of nitric oxide-releasing nonsteroidal anti-inflammatory drugs (NO-NSAIDs) as well as ESD, narrow-band illumination, fluorescence endoscopy, confocal endoscopy and natural orifice transluminal endoscopic surgery (NOTES) as major advances, and is looking forward to future development of NOTES as well as robotic capsular endoscopy. However, he admits that we still need to clarify NSAID and aspirin-related

upper GI bleeding. For example, if bleeding occurs, how long should we stop these drugs without any thrombotic event in the heart or brain? Jaw-Town Lin says we need to develop new NSAIDs that do not have cardiovascular or GI side effects, or require co-therapy with gastro-protective agents.

Other issues highlighted by Jaw-Town Lin include: how to treat GIST if imatinib fails; how to eradicate *H. pylori* if levofloxacin plus ribabutin fails; biomarkers for predicting high-risk subjects developing NSAID-induced gastropathy; biomarkers for predicting high-risk gastroesophageal reflux patients unresponsive to proton pump inhibitor therapy; cost-effectiveness of eradicating *H. pylori* as a chemoprevention measure against gastric cancer; cost-effectiveness of endoscopic resection of colorectal adenomatous polyps as a chemoprevention measure against colorectal cancer; evaluation of quality-of-life for extensive operation of advanced GI cancers in geriatric patients.

Functional gastrointestinal disorders

The management approach, that of adopting a biopsychosocial model to understand and tackle functional gastrointestinal disorder (FGID) symptoms has been a major advance, says John McLaughlin (*University of Manchester, Manchester, UK*). By way of analogy, he states that in ischemic heart disease, no-one would have a problem with understanding risk/therapy as tackling a combination of factors (stress, diet, smoking, blood pressure, lipids, with underlying genetic risks). Yet until recently a narrow singularity remained in FGIDs, evidenced by investigators looking for abnormal 'motility' or 'visceral hypersensitivity' as the basis of the disorders. On the other hand, the realization that a key disease mechanism/target does not exist explains the disinvestment of most big pharmaceutical companies from FGIDs recently. Future developments should include agents for visceral pain that are effective, nonconstipating and lack central/addictive adverse properties, he believes.

Doug Taupin believes we need effective well-tolerated and safe therapy for d-IBS and c-IBS, effective well-tolerated and safe prokinetic agents for idiopathic and diabetic gastroparesis, and effective medical therapy for acute severe pancreatitis. John McLaughlin adds that investigative

approaches to truly separate and distinguish central (brain/spinal) from peripheral (GI) mechanisms in the genesis of GI symptoms, especially pain are required. Also, as a fine point, we need to understand what really causes bloating!

John McLaughlin expresses concern that expert panels such as the Rome group continue to classify and reclassify (and recently re-reclassify) FGID patients according to symptom patterns whereas it would be more apt to try and dissect/classify them pathobiologically [e.g., central [including psychological] *vs* peripheral (inflammation, postinflammation, immune/allergic, food intolerance, dysbiosis, stress and the gut)]. Just lumping people, for example as 'diarrhoea' or 'constipation' predominant IBS will never tackle this problem, he continues. Indeed, using pharmaceutical agents as probes may be more rational. Thus, if a small percentage has a serotonergic abnormality they will be teased out by smarter use of medications.

Lower gastrointestinal tract

Doug Taupin regards the mesalazine phase 3 study, which showed effective postprimary prophylaxis for diverticulitis, as an important study, as well as the treatments for inflammatory sarcopenia (such as seen in Crohn's disease (CD)) [Burnham *et al.* 2005], and the role of TNF α inhibitor drugs [Cai *et al.* 2004]. Tsutomu Chiba and Massimo Campieri (*University of Bologna, Bologna, Italy*) highlight the use of TNF α inhibitors as a significant advance in treating inflammatory bowel disease (IBD). This was echoed by Uma Mahadevan-Velayos (*University of California, San Francisco, CA, USA*) who remarked that there are now three TNF α inhibitor drugs and an alpha-integrin agent (natalizumab) approved for use in CD. She points out that the COMMIT trial at DDW shows that combination immunomodulator plus infliximab is not better than infliximab alone [Feagan *et al.* 2008]. A future focus, she adds, will be to find novel mechanisms to target drug therapy in CD and ulcerative colitis (UC) [e.g., IL-17, IL-12/p40, etc]. Tsutomu Chiba expects that future treatment options for IBD will be increased and improved.

Concerns about IBD therapy, according to Doug Taupin, are the lack of randomized comparison studies on biologicals in CD, lack of clarity on the

relative place of TNF α inhibitors *vs* integrin antagonists, and the deficiency of specific UC therapy (i.e., CD-directed therapy is less effective in UC). Dr Mahadevan-Velayos continues that there are many unanswered questions: When should we start biologic therapy – early or after other therapies have failed? What is the safety of long-term biologic use (e.g., >5 year data, >10 year continuous use data)? She concludes that a good noninvasive marker of disease activity is needed for IBD – CRP and fecal calprotectin can be helpful but we need something better.

IBD prevention is an issue that Tsutomu Chiba would like to see resolved, while Massimo Campieri adds that nutrition needs to be looked at to see if it can improve IBD symptoms. He says we should attempt to identify the bacteria and viruses that may be responsible for exacerbating IBD, and understand their interaction with the gut wall. A further area to investigate is the impact that proton pump inhibitors may have on the lower bowel. He is keen to explore the inflammatory effect that continued acid suppression might have on the lower bowel.

Gastrointestinal cancers

John Carethers (*University of California, San Diego, CA, USA*) points out that specific targeted therapies (small molecules) are a major advance for GI cancer treatment as well as advances in imaging (endoscopic ultrasound), and in the endoscopic resection of tumors. He believes there will be continued discovery of small molecules for cancer, and also sees the need for cross-training of gastroenterologists as oncologists. He also hopes for a major breakthrough in the treatment of pancreatic cancer and a significant boost in the screening numbers for colorectal cancer. Better treatment and early diagnosis of pancreatic cancer are issues that need resolving, according to Dan Chung (*Massachusetts General Hospital, Boston, MA, USA*) and Tsutomu Chiba.

Dan Chung lists the most significant recent advances as: genetic testing for hereditary GI cancer syndromes; new chemotherapeutic regimens in colorectal cancer that have significantly improved survival (e.g., FOLFOX [folinic acid, fluorouracil, oxaliplatin], vascular endothelial growth factor [VEGF] inhibitors, epidermal growth factor receptor [EGFR] inhibitors);

widespread implementation of colorectal cancer screening in the USA; development of new of colorectal screening tests; and, the success of cox-2 inhibitors for colorectal chemoprevention. He sees the future advances as: enhancement of colorectal screening modalities to increase accuracy and compliance; cancer risk stratification with molecular/genetic markers; biomarkers; and, targeted agents for cancer treatment. We need to see an improvement from 35 to 40% eligible for colorectal cancer screening to at least 60%, says John Carethers. Jaw-Town Lin predicts there will be future cytokine antibody and anti-inflammatory steroid therapy for GI cancers associated with inflammation.

Tsutomu Chiba agrees that combination treatments for GI cancers (e.g., FOLFOX or FOLFIRI [folinic acid, fluorouracil, irinotecan] plus bevacizumab for colon cancer, and cisplatin plus TS1 for gastric cancer) have improved therapy considerably, and he also commends the endoscopic treatment of gastric and esophageal cancer. He says that, in Japan, there are still 120,000 gastric cancer patients and among them only 50,000 die. More than half of the remaining 70,000 patients are rescued by endoscopic treatment. In the future, he sees both endoscopic treatment and chemotherapy as very promising. Therapy is slowly improving, says John Carethers, and we are lengthening survival of patients; however, sometimes, it does not come fast enough for some patients.

Hepatology

The expansion of the class of nucleoside and nucleotide inhibitors of hepatitis B virus (HBV) with entecavir and tenofovir is seen as a major advance by Donald Jensen (*University of Chicago Medical Center, Chicago, MI, USA*) and Dan Pratt (*Massachusetts General Hospital, Boston, MA, USA*). These agents may produce complete suppression of HBV replication in almost every patient, and they have an extremely low probability of resistance. By way of example, Doug Taupin comments that entecavir has a low rate of drug resistance in nucleoside-naïve chronic HBV-infected patients, but is less effective in lamivudine-refractory patients. The addition of these drugs will lead to a major decrease in clinical endpoints caused by chronic HBV infection, comments Heiner Wedemeyer

(*Medizinische Hochschule Hannover, Hannover, Germany*).

Ken Sherman (*University of Cincinnati, Cincinnati, OH, USA*) believes that the development of new small molecule agents in the protease and polymerase classes has been a significant advance for hepatitis C virus (HCV) treatment. David Nelson (*University of Florida, Jacksonville, FL, USA*) agrees with this and adds they will likely lead to doubling of cure rates, shorter duration of therapy (3–6 months), and fewer side effects. He adds that the development of specifically-targeted antiviral treatments for hepatitis C (STAT-C) and their potential impact on future therapies is also a step forward. In addition, one may be able to consider non-interferon (IFN) regimens in the next five years. Completion of development of small molecules for HCV is regarded by Ken Sherman as an important future step in HCV therapy.

The concept of individualized treatment with pegylated IFN and ribavirin for chronic HCV infection is becoming a reality, according to Donald Jensen, made possible by the use of viral kinetics to identify rapid, early and slow responders in each of the four major genotypes (1, 2, 3, and 4). Therapy may now encompass not only different drug dosages, but also treatment durations. Several future advances will have the capability of altering the paradigm of treatment, he continues, notably, the continuing development of STAT-C incorporating a variety of small molecule viral inhibitors. Furthest along are the HCV protease inhibitors (telaprevir and boceprevir). In phase 1b and 2 clinical trials, these agents, when combined with peg-IFN and ribavirin, almost double the sustained viral response rates with a shorter duration of treatment (24 *vs* 48 weeks). Heiner Wedemeyer agrees and states that they are now entering phase 3 trials and will be licensed in 2011/2012, thus leading to a substantial increase in HCV clearance rates and shortening of IFN-based therapy. A drawback according to Doug Taupin, however, is that they still need to be given with full-dosage ribavirin with associated side effects.

Other agents in the pipeline include HCV nucleotide polymerase inhibitors and cyclophilin inhibitors. Donald Jensen is also encouraged by the recent description of the efficacy of

nitazoxanide to decrease relapse rates associated with the treatment of HCV genotype 4 (Rossignol *et al.* 2007).

Another FDA approval highlighted by Donald Jensen is oral sorafenib in hepatocellular carcinoma (HCC). It is the first agent of its kind to demonstrate significant antitumor activity. David Nelson believes this will lead to an explosion of interest and trials in HCC and he predicts that we will see the emergence of an oncology focus within the hepatology community and a new oncology training of future GI/hepatology physicians.

There are significant issues that will need to be resolved as we determine the most effective way to use the newer therapies to both improve outcomes as well as avoid emerging viral resistance, says Dan Pratt. Other current concerns surrounding HCV therapy include drug interactions, their maximum efficacy, and their efficacy in special groups (e.g., HIV/HCV coinfection, decompensated, nonresponders), according to Ken Sherman.

Looking at future requirements, Heiner Wedemeyer, states that we need to develop an effective treatment against hepatitis Delta, the most severe form of viral hepatitis affecting 20 million people worldwide. Prevention of HCV reinfection after liver transplantation, and the development of a vaccine against hepatitis C are all issues we need to address in the future, he adds.

Other advances will be the identification of the role of obesity and the metabolic syndrome (insulin resistance) in potentiating hepatic fibrosis and carcinogenesis, says Donald Jensen, and we need to find suitable treatments for nonalcoholic fatty liver disease (NAFLD) as well as nonalcoholic steatohepatitis (NASH), adds Doug Taupin [Torres and Harrison, 2008]. David Nelson agrees and states that we also need better liver cancer screening tools and surveillance regimens.

A new focus of biomarkers for liver fibrosis will likely lead to the replacement of liver biopsy for staging purposes, suggests David Nelson. All data suggest that liver elastography and serum fibrosis markers are viable noninvasive tools for staging fibrosis, he says.

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Conflict of interest

None declared.

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