Medicom International Conference Series in Gastroenterology

UEG Week 2019

United European Gastroenterology

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PEER-REVIEWED CONFERENCE REPORT

First-in-Human Radio-frequency Vapor Ablation in Barrett's Oesophagus

In an initial patient series for pre-clinical testing, radiofrequency vapor ablation appears to be safe and effective for ablating Barret's oesophagus dysplasia.

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Editor Prof. Joost Drenth, Radboudumc Nijmegen, the Netherlands

Letter from the Editor

Prof. Joost Drenth

Dear Reader,

The UEG Week 2019 -advancing science - linking people- is arguably the yearly focus point of European gastroenterology bringing together practitioners, top scientists and everyone interested in digestive health. As such, it serves as a true educational hub showcasing key developments in the field and contributing to the postgraduate teaching of gastroenterologists.

This year >13,000 participants from >122 countries contributed to the success of UEG Week 2019. More than 4,000 scientific abstracts were sent to the UEG and the best made the cut and were presented at the UEG Week in Barcelona, Spain. We are looking back at 5 intensive days of scientific interaction, networking and learning. The meeting is unique in that part of the program is offered through online live streaming and this year there were almost 4,200 viewers.

In case you have missed some of the exciting content there is a possibility to go back online as all UEG Week highlight sessions are available on demand. Here, we present the best of the best that was offered from the UEG Week 2019. We have been careful to select the work that is likely to impact your clinical practice and has the potential to influence your clinical thinking.

Best,

Joost PH Drenth

Biography

Joost PH Drenth is a Hepatologist and the current chair of the Department of Gastroenterology and Hepatology of the Radboudumc, Nijmegen, the Netherlands. He received his medical degree from the University of Maastricht and his PhD (cum laude) at the Radboudumc. He was trained as an Internist and Gastroenterologist at the Radboudumc. He obtained a Royal Netherlands Academy of Art and Sciences fellowship and was a research fellow at the National Institutes of Health, Bethesda, USA. He serves and has served within a number of committees of professional organisations at the national as well as the European level, most notably United European Gastroenterology (Vienna, Austria). He is the chair of the Dutch Society for the study of Liver disease. He is the current editor of the UEG journal. He acts as the pillar head in the European Rare diseases Network (ERN) Liver consortium.

Conflict of Interest Statement:
JD declares that The Radboudumc, on behalf of JD, received honoraria or research grants from Novartis, Otsuka, Merck, Gilead, and Abbvie. JD has served as consultant for Celltrion, Gilead and Abbvie, and has been member of advisory boards of Otsuka, Gilead, and Abbvie.

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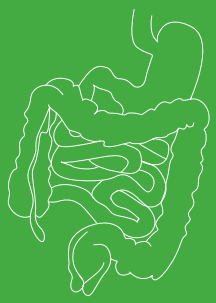

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MEDICOM MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

"We are trying to reduce the burden of digestive diseases"

Interview with UEG president
Prof. Paul Fockens,
conducted on 29 October 2019 by Dr Rachel Giles

Prof. Paul Fockens (Amsterdam University Medical Center, the Netherlands) is Professor and Chair of Gastroenterology, Hepatology and Gastrointestinal Endoscopy and current President of the United European Gastroenterology.

How did you find this year's UEG Week?
I think the conference was a big success again, maybe even better than in previous years. What typically goes very well at this conference is the multidisciplinary nature; we have a number of other societies that participate, so there is not a single session which is not characterised by multi-disciplinary aspects. We met our goal of having over 13,000 participants, which was a very nice turnout, and we had a fantastic multidisciplinary post-graduate course programme as well. Over 4,000 people participated in the Saturday and Sunday courses held before the actual meeting, which represents a tremendous growth in attendance observed over the last few years.

The UEG covers more than just the annual conference, can you discuss the vision of the UEG?
The idea is to improve the knowledge of gastroenterology throughout medicine. We try to increase the knowledge, if you look at the more political part of it, the public affairs part of it, we try to reduce the burden of digestive diseases and improve digestive health, so we also look at prevention. The UEG Week is the biggest event we hold, obviously it is a very important event for us, but we also use a lot of UEG resources to invest in research, in public affairs, in education, and all the other things we do.

Given that resources are limited, what are the UEG priorities?
What the UEG tries to do is raise the level of GI knowledge to support integration of subspecialties, taking it to a level of collaboration, instead of individual silos. Gastroenterology, in particular, has a lot of silos, such as liver disease, endoscopy, etc; there are 17 sub-specialty societies that participate in the UEG. The danger with silos is that they each may think that their area is the most important one. And of course, while we recognise that each subspecialty is individually important, overall, if we want to make an impact for patients in general with GI problems, then we should not look at the small sub-parts, but we should look at the whole of the United European Gastroenterology.

How would you compare the UEG to other global counterparts?
In general, UEG focusses on interdisciplinary work only, whereas the North American Digestive Disease Week serves individual programmes in each subspecialty. The UEG Week only advances research across subspecialties. Although each smaller specialty has its own programme, the UEG specialises in transcending specialist information and integrating the themes that run across specialties.

Globally, all of our colleague organisations need to focus more on education and prevention. One topic, for example, that has been under-researched in the last 20-30 years is nutrition. Happily, we are now experiencing a trend shifting focus towards nutrition again.

And then there are topics of a more specialist and experimental nature, such as trends in topics like microbiomics, in addition to all the -omics in the last years. While I think it is a nice area for research, the question remains how we can implement these developments into routine clinical practice. Although I am not sceptical, I do pragmatically believe that it will take 10 years for this research to adequately develop to reach clinical practice.

Take-home messages:
Go to the web site and look at the huge amount of educational material and opportunities there are outside the UEG Week meeting, including research opportunities. Not everyone can attend the UEG Week meeting, but the main events and news can be easily found on our webpage. The UEG aims to cover the scope of all specialties in the gastroenterology field and provide a framework for inter-specialty collaboration.

Upper GI Disorders

Locally active corticosteroid promising in eosinophilic oesophagitis

Orodispersible budesonide delivered specifically to the oesophagus as a tablet was effective in inducing clinical and histological remission in patients with eosinophilic oesophagitis, according to the data from the EOS-2 trial, reported by Prof. Alfredo Lucendo (Tomelloso General Hospital, Spain) [1].

EOS-2 aimed to test the efficacy of a 6-week open-label induction treatment with oral budesonide (1 mg, twice daily) in a large prospectively treated cohort of eosinophilic oesophagitis patients, which was used as a feeding arm for the further double-blind maintenance phase of the EOS-2 trial, not reported here. Prof. Lucendo presented the induction phase data.

Orodispersible budesonide targets eosinophilic inflammatory infiltrate by preventing antigen-stimulated secretion of proinflam-matory signal molecules into the oesophageal epithelium. The drug is dissolved against the hard palate and swallowed slowly. The study recruited 181 adults with clinical and histological active eosinophilic oesophagitis refractory to standard doses of various proton pump inhibitors, who were then treated in the 6-week induction phase with budesonide. The primary endpoint and basis for later randomisation into the double-blinded maintenance phase was based on both clinical and histological factors, requiring patients to achieve both clinical remission (≤2 points on numerical rating scales (0-10 points) each for dysphagia and odynophagia on each of the 7 days prior to end-of-treatment) in addition to histological remission (peak eosinophil count <16 eosinophils/mm^2 high power field).

At 6 weeks, 69.6% (126/181) of patients were in complete clinical and histological remission. Compared to baseline, oral budesonide twice daily achieved all assessed clinical, endoscopic, and histological endpoints. Prof. Lucendo underscored that the findings from EOS-2 recapitulated the results from the smaller double-blinded, placebo-controlled EOS-1 study (n=88; 58% achieved complete remission in the budesonide arm vs 0% in the placebo arm), but in a larger independent cohort.

First-in-human radiofrequency vapor ablation in Barrett's oesophagus

In an initial patient series, radiofrequency vapor ablation (RFVA) appears to be safe and effective for ablating Barret's oesophagus dysplasia. Dr Sanne Noortje van Munster (St. Antonius Hospital, Nieuwegein, the Netherlands) presented the results of the preclinical and first-in-human data [1].

Radiofrequency ablation (RFA) is highly effective in the ablation of dysplastic Barrett's oesophagus. However, for optimal contact with the oesophageal wall, multiple deployment steps and/or multiple treatment endoscopies may be required. To try and solve that problem, AquaMedical's RFVA system generates vapor/steam at 100°C using an RF electrode at the catheter tip to ablate tissue. The 7Fr RFVA catheter is passed through the biopsy channel of a standard endoscope with distal attachment cap and is used to create focal (~1 cm^2) ablations in the oesophagus. In this study, the investigators sought to produce preliminary data with regard to RFVA safety and efficacy in patients with flat dysplastic Barrett's oesophagus.

The RFVA system was tested for feasibility in three models. Firstly, the researchers used an *in vitro* lean-beef model to test increasing doses of RFVA and increasing numbers of RFA applications (total 10 ablations/modality/dose), which both resulted in increasing depth of ablation. The range of ablation depth with 2–5s vapor (0.75 mm–1.5 mm) was comparable to 1–4× RFA applications (0.58 mm–1.5 mm). With this knowledge, they then tested RFVA in a subacute porcine study (n=6). No differences were found between any doses and treatments tested on the pigs (3/5s vapor and 1–2× RFA), and no complications occurred. However, the researchers noted that the 3s RFVA was comparable to 2× RFA, whereas 5s RFVA produced slightly deeper ablation. Based on the porcine data, the researchers selected a conservative 1s and 3s dose for human testing.

In the ongoing first-in-human study, a total of 42 RFVAs were applied in 12 patients. Per-patient, 4 ablations (2/dose) were applied at 1 cm distance. No adverse events occurred and patient-reported pain scored only 0–1 out of 10 during 14

1. Lucendo A et al. UEG Week 2019, Abstract OP091.

days post-treatment. Follow-up endoscopy was performed in 6 patients and showed a median squamous conversion rate for the 1s and 3s ablations of 73% and 98%, respectively. Biopsies of endoscopically eradicated areas showed histologically normal squamous epithelium.

In conclusion, in this first preliminary series of patients, the Aqua RFVA system was safe for oesophageal ablation and successfully converted dysplastic Barrett's oesophagus into histologically normal squamous epithelium.

1. Van Munster S et al. UEG Week 2019, Abstract LB09.

Irritable Bowel Syndrome

Faecal microbiota transplantation is effective for irritable bowel syndrome

The results of a double-blind, randomised, placebo-controlled study have confirmed that faecal microbiota transplantation (FMT) is an effective and well-tolerated treatment for irritable bowel syndrome (IBS), provided the donor is carefully selected.

Prof. Magdy El-Salhy (Haukeland University Hospital, Norway) reported high rates of clinical response and marked symptom improvements in a large cohort of patients with various subtypes of IBS [1]. The investigators used several novel methodologies, and highlighted the importance of donor selection for optimising the effectiveness of FMT as a treatment for IBS by using frozen samples from a single 'super-donor' on individuals in the current study. "We set out to optimise our chances of treatment success by selecting a single, well-defined donor who fulfilled European guidelines for FMT donors, and who had a favourable faecal microbial profile," Prof. El-Salhy explained.

The study randomised 164 individuals with IBS and moderate-to-severe IBS symptoms to receive either 60 g placebo solution (derived from the patient's own faeces), a 30 g donor transplant solution, or a 60 g transplant solution. Unlike in previous studies, the transplant material had been stored frozen (-80°C/-112°F), and was administered into the proximal duodenum with a gastroscope after thawing. This approach avoids the need for bowel preparation prior to transplantation, thereby making it more amenable to daily clinical practice. The primary efficacy endpoint of the study was the percentage of patients who achieved a 50-point reduction in IBS-Symptom Severity Score at 3 months after FMT.

A response to FMT treatment was observed in 23.6% of individuals who received placebo, 76.9% of individuals who received a 30 g transplant, and 89.1% of individuals who received a 60 g transplant. Clinically significant symptom improvement (i.e. a reduction in IBS-Symptom Severity Score) occurred in 5.5%, 35.2%, and 47.3% of individuals in the placebo, FMT 30 g, and FMT 60 g treatment groups, respectively. Significant improvements in fatigue (Fatigue Assessment Scale) and quality of life (IBS-QoL instrument) were also observed in the FMT treatment groups compared with the placebo group. An analysis of faecal bacterial profiles showed changes in the abundance of different bacteria in the two FMT groups, but not in the control group.

Adverse events after FMT occurred in about 20% of patients and were mild and self-limiting gastrointestinal symptoms such as abdominal pain, diarrhoea, or constipation, usually occurring intermittently in the first 2 days following FMT.
Prof. El-Salhy and colleagues believe this study confirms that FMT is an effective treatment for IBS, but stress the importance of using a "super-donor" to achieve treatment success. The use of frozen faeces eliminates the logistical problems associated with FMT involving fresh faeces, making it possible to establish biobanks for the routine use of FMT in clinical practice.

1. El-Salhy M. UEG Week 2019, Abstract OP004.

Human milk oligosaccharides improve IBS symptoms

Compounds that are structurally identical to human milk oligosaccharides (HMOs) can significantly improve irritable bowel syndrome (IBS) symptoms within 4 weeks.

Dr Olafur Palsson (Chapel Hill, North Carolina, USA) presented the 12-week trial, which recruited 317 subjects from 17 sites across the United States (70.7% females; mean age 44.0 years, range 18-93 years) [1]. Participants all had a diagnosis of IBS with Rome IV criteria. Study participants orally consumed 5 g of a 4:1 powder mix of 2'fucosyllactose (2'FL) and lacto-N-neotetraose (LNnT) daily for 12 weeks. Primary outcomes were patient-logged bowel habits, IBS symptoms, and quality of life at baseline followed by every 4 weeks during the study period.

Of the 317 subjects who received the HMOs, 136 reported constipation at baseline, 85 with diarrhoea, 95 with mixed constipation/diarrhoea, and 1 with unspecified IBS. From baseline to 12 weeks, all 245 participants in the intention-to-treat analyses demonstrated a significant reduction in total percentage of abnormal bowel movements (Bristol Stool Form Scale types 1, 2, 6, or 7; 89.8% [95% CI 88.1–91.5] vs 54.9% [95% CI 51.4–58.4]). Furthermore, the secondary outcomes of the IBS-Symptom Severity Score (mean 327 vs 128), abdominal pain severity (mean 62.5 vs 25.4), bloating severity (mean 56.8 vs 23.2), and improvement in health-related quality of life (mean IBS-QoL scores 50.4 vs 74.6) were also all improved. Within 4 weeks, 77% of subjects reported significant improvement in symptom severity. At 12 weeks, 87% saw a clinically significant reduction in symptom severity, specifically:

- 59% reduction in abdominal pain severity;
- 59% decreased bloating;
- 58% reduced days with abdominal pain; and
- 37% decreased number of abnormal stools.

The authors concluded that the findings in this new study support the value of microbiota-directed therapies, such as the inclusion of prebiotic HMOs in IBS dietary planning, although randomised controlled trials are still needed.

1. Palsson O et al. UEG Week 2019, Abstract OP201.

Inflammatory Bowel Disease

Practice-changing: infliximab in children with Crohn's

Top-down infliximab is superior to step-up treatment in children with newly diagnosed moderate-to-severe Crohn's disease (CD).

Dr Lissy de Ridder (Erasmus University Medical Center, Rotterdam, the Netherlands) presented the practice-changing results of the multicentre open-label randomised controlled TISKids study [1]. The study aimed to acquire early control of the inflammatory cascade by inducing early mucosal healing an preventing the accumulation of bowel damage characteristic of the disease. The investigators' hypothesis was that initiation of infliximab directly after diagnosis in moderate-to-severe paediatric CD patients would prevent the inflammatory cascade, and result in disease control.

Children (n=97) between the ages of 3-17 years with untreated moderate-to-severe CD (defined as a weighted paediatric CD activity index (wPCDAI) >40) were randomised to one of 2 arms: the top-down arm treated with infliximab biosimilar CT-P13 vs the step-up treatment arm. The top-down group (n=50) received 3 infusions of infliximab in the first 6 weeks and 2 maintenance doses at weeks 14 and 22 while being supported by azathioprine for the entire 52 weeks. Patients in the step-up arm started with either prednisone (n=19) or exclusive enteric nutrition (n=28), in addition to azathioprine. Endoscopy was performed at 10 weeks (required) and voluntarily at 52 weeks. Treatment intensification was allowed under certain conditions. Primary non-response was defined as no response at week 6 compared with baseline with the decrease in wPCDAI of <17.5. A secondary loss of response was defined as either an increase of wPCDAI of >17.5 or a total wPCDAI score of >40 after response had already been achieved. The treatment was intensified with (re)start of corticosteroids, (re)start of biological treatment, or intensification of infliximab scheme with a dose intensification or treatment adjustment. The primary endpoint was clinical remission with a wPCDAI score <12.5 at week 52 without the need for additional CD-related

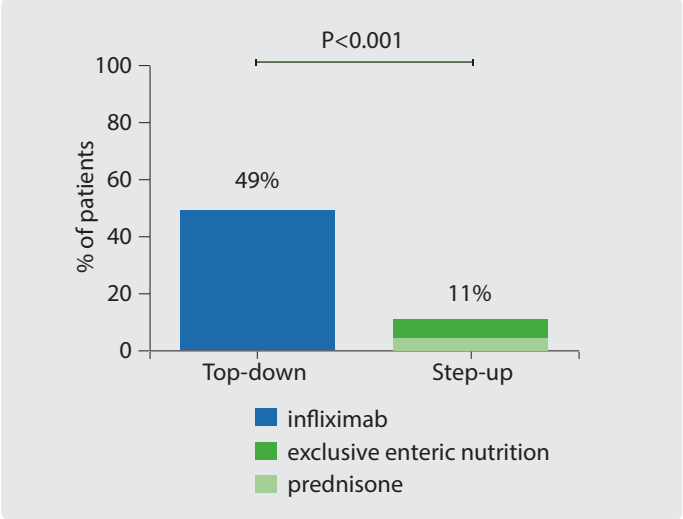
therapy or surgery. Secondary endpoints were mucosal healing rates at week 10, as measured by calprotectin levels, and confirmed by endoscopy, as well as the cumulative therapy use (e.g. steroids, biologicals).

Endoscopic imaging at week 10 indicated that infliximab provided a significant clinical benefit in mucosal healing; 61% of remission the patients in the top-down group had endoscopic remission vs only 14% of the step-up group (P=0.001). The top-down group also had significantly decreased levels of inflammatory markers such as CRP (P=0.008), ESR (P=0.001), leukocyte counts (P<0.001), and calprotectin levels (P=0.001). At week 52 the primary endpoint was met, with 49% of the top-down group in full clinical remission, as opposed to 11% of the step-up group (P<0.001) who did not require additional treatment or surgery (see Figure). The patients in the step-up arm also required earlier and more frequent interventions with treatment intensification (P=0.001).

Dr de Ridder pointed out that all patients will be followed up for 5 years, and the true value of early intervention in modifying the inflammatory cascade will only be clear with longer term results. In addition, detailed immunological profiling of all patients will hopefully help stratify patients into those that may benefit from a given treatment; the fact that 11% of the step-up group did achieve remission at 52 weeks suggests that there may be a risk for overtreatment in certain individuals.

1. De Ridder L et al. UEG Week 2019, Abstract OP001.

Figure. Patients in clinical remission (wPCDAI score <12.5) without treatment intensification at week 52 [1]



Ustekinumab is safe and effective in ulcerative colitis: 2-year data

New 2-year data from the long-term extension of the phase 3 UNIFI study demonstrates the efficacy and safety of ustekinumab through 2 years of treatment in adults with moderately to severely active ulcerative colitis (UC).

These data, presented by Prof. Bruce Sands (Icahn School of Medicine at Mount Sinai, New York, USA) as a late-breaking data abstract [1], included 399 participants who were in clinical response 8 weeks after receiving a single intravenous induction dose of ustekinumab and who were then randomised to receive ustekinumab subcutaneous 90 mg injections every 12 weeks, ustekinumab SC 90 mg injections every 8 weeks, or placebo, and who were treated in the long-term extension.

Results showed that the majority of patients were able to sustain remission through week 92 as assessed by symptomatic remission. The percentage of patients receiving ustekinumab subcutaneous who were in symptomatic remission between weeks 44 and 92 ranged from 83-90%. Among patients who had achieved clinical remission at maintenance baseline, 69% of patients receiving ustekinumab every 8 weeks and 80% of patients receiving ustekinumab every 12 weeks maintained symptomatic remission at both weeks 44 and 92. Additional analyses demonstrated that approximately 60% of patients receiving ustekinumab every 8 or 12 weeks achieved corticosteroid-free symptomatic remission at week 92 (64.3% and 63.8%, respectively).

Through 2 years, the proportions of patients with adverse events (AEs), serious AEs, and serious infections in the ustekinumab groups were generally comparable with the placebo group. No new safety signals were observed. Ustekinumab has demonstrated a consistent safety profile in UC where trials show the treatment is well tolerated. In the primary randomised population of the induction and maintenance studies, a similar proportion of patients in the ustekinumab and placebo groups experienced AEs, serious AEs, infections, and serious infections through to week 44. During the induction phase, 1 death from an oesophageal varices haemorrhage was reported, and no malignancies, opportunistic infections, or tuberculosis were reported. During the maintenance phase, no deaths and 2 malignancies other than non melanoma skin cancer (NMSC) were reported (90 mg ustekinumab every 8 weeks: colon cancer n=1; 90 mg

ustekinumab every 12 weeks: papillary renal cell carcinoma n=1). There was 1 patient-reported NMSC in the group receiving 90 mg ustekinumab every 12 weeks (2 squamous cell carcinoma events).

1. Sands BE et al. UEG Week 2019, Abstract LB01.

Ileal microbiota predict recurrence in CD patients after resection

A new study, led by researchers from Saint Antoine Hospital, in France, reveals that ileal mucosa-associated microbiota may help predict recurrence in patients with CD after ileocecal resection [1].

Recurrence of inflammatory lesions is frequent in patients undergoing ileal resection for Crohn's disease (CD), although there is not a single clinical risk factor that can be used as a perfect predictor of early postoperative endoscopic recurrence. The researchers of this study sought a microbiotic biomarker to predict recurrence. To this end they catalogued the ileal mucosa-associated microbiota by using ribosomal 16S sequencing at the time of surgery and/or at the time of postoperative endoscopic evaluation (about 6 to 12 months after surgery) in 201 patients from 9 centres in the prospective REMIND cohort. Not surprisingly, antibiotics treatment within one month before surgery had a dramatic impact on microbiota composition (P<0.0001) and diversity (Shannon index mean 4.3±0.1 vs 3.7±0.2, P=0.006).

The ileal mucosa-associated microbiota exhibited major changes following CD surgery that differed between the time of surgery and the time of postoperative endoscopic evaluation. Specifically, changes included a decrease in beta diversity and a decrease in the *Gammaproteobacteria* class, an increase in the *Alphaproteobacteria* class, a decrease in the *Bacilli* class and an increase in the *Clostridiales* order.

Compared with patients who did not recur, however, endoscopic recurrence was associated with a high abundance of bacteria from the *Gammaproteobacteria*, the *Ruminococcus* gnavus group and *Corynebacterium* genera (area under the curve: 97.1% [93.8%-100%] and 81.0% [60.8%-100%] in the whole population and in the validation set respectively). In contrast, patients without endoscopic recurrence at 6 to 12 months after surgery showed increased levels of bacteria from the *Lachnospiraceae* families, such as the *Roseburia*, *Blautia* and *Dorea genera*.

In conclusion, ileocecal resection and endoscopic recurrence are associated with changes in ileal mucosa-associated microbiota, which may be applied for prognostication.

1. Sokol H et al. UEG Week 2019, Abstract OP209.

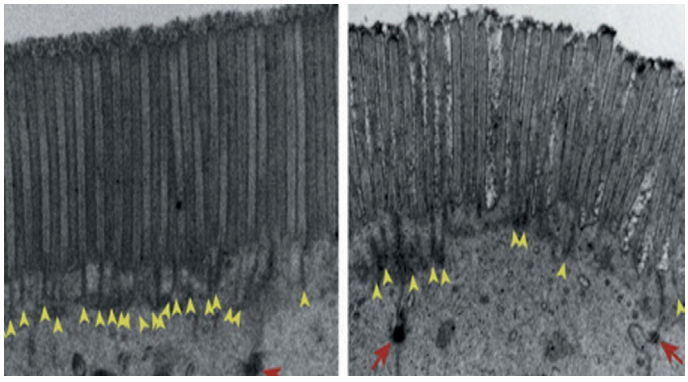
Decreased microvilli length in CD patients

Decreased microvilli length, as a result of decreased expression of genes encoding key microvilli-specific products, might contribute to epithelial malfunction contributing to disease progression in patients with Crohn's disease (CD).

Pathologist Prof. Thaddeus Stappenbeck (Washington School of Medicine at St Louis, Missouri, USA) and his team examined healthy regions of intestinal tissues from patients with CD to identify defects that might contribute to pathogenesis and chronicity of inflammatory bowel diseases [1]. Performing RNA sequencing from formalin-fixed paraffin-embedded ileal tissue sections of 36 patients with CD and 32 individuals without CD, the researchers catalogued the expression changes between inflamed and uninflamed tissues from the same patient. The researchers then developed methods to visualise an overlapping modular network of genes dysregulated in the samples and validated their findings using biopsy samples from the UNITI-2 phase 3 trial of ustekinumab for patients with CD and healthy individuals.

Using cluster analyses, the researchers found a cluster of genes encoding proteins associated with the enterocyte brush border to be significantly downregulated, leading them to investigate microvilli. A separate set of samples (3 control

Figure. Electron micrograph of microvilli. Left panel, healthy control patient, right panel, microvilli from a CD patient [1]



and 4 CD samples) was analysed by transmission electron microscopy (see Figure), in which they validated in all CD samples that the microvilli were shorter and less organised than in the control samples. The expression of microvilli genes correlated with microvilli length and endoscopy score and was also associated with response to treatment with ustekinumab. This research warrants follow-up to evaluate causality vs effect.

1. Stappenbeck T et al. UEG Week 2019, Abstract LBA03.

Phase 2 data shows benefit for mirikizumab in CD patients

Patients with Crohn's disease (CD) treated with mirikizumab for induction therapy experienced improvements to clinical and endoscopic outcomes.

"Mirikizumab is a humanised immunoglobulin G4 monoclonal antibody, and it binds to the p19 subunit of IL-23," Prof. Bruce Sands (Icahn School of Medicine at Mount Sinai, New York, USA) began his presentation [1]. "We assessed the safety and efficacy of mirikizumab with a phase 2, multicentre, randomised, parallel-arm, double-blind, placebo-controlled trial in patients with moderate-to-severe CD." Mirikizumab has also shown some success in treating ulcerative colitis and psoriasis.

Researchers randomly assigned 191 patients to receive either 200 mg (n=31), 600 mg (n=32), or 1,000 mg (n=64) of mirikizumab versus placebo (n=64) intravenously at weeks 0, 4, and 8. The primary outcome of the study was to determine the superiority of mirikizumab over placebo at week 12, as assessed by at least 50% reduction of the validated Simple Endoscopic Score for CD (SES-CD). Secondary outcomes were clinical remission and CD activity index.

At week 12, the 200 mg group achieved a 25.8% endoscopic response rate (95% CI 10.4–41.2, not significant), the 600 mg group achieved a 37.5% response rate (95% CI 20.7–54.3; P=0.032), and the 1,000 mg group achieved a 43.8% response rate (95% CI 31.6–55.9; P=0.009), whereas in the placebo arm only 10.9% of patients achieved endoscopic response (95% CI 3.3–18.6). Clinical remission assessed by patient-reported outcomes was also greater in treatment groups compared with placebo (12.9%, 28.1%, and 21.9% vs 6.3%, respectively). All 3 treatment groups showed greater response regarding CD activity index (200 mg: P=0.015; 600 mg: P=0.001; 1,000 mg: P=0.026).

The safety findings of the study did not reveal any new signals from the safety profile known for mirikizumab, with the frequency of serious and treatment-emergent adverse events in all 3 treatment arms similar to placebo.

1. Sands BE et al. UEG Week 2019, Abstract OP166.

Subcutaneous ustekinumab as maintenance therapy in UC

Subcutaneous ustekinumab every 8 or 12 weeks achieved clinical remission in ulcerative colitis (UC) patients as maintenance therapy after receiving a single ustekinumab induction dose. The safety for ustekinumab in UC patients was consistent with the known safety profile of ustekinumab.

Prof. Silvio Danese (Humanitas University, Milan, Italy) presented the phase 3, double-blind, randomised withdrawal study in patients with moderate-to-severe active UC who failed conventional or biologic therapy and who had a clinical response 8 weeks after receiving a single ustekinumab intravenous induction dose [1]. Patients (n=523) were randomised 1:1:1 at week 0 to receive subcutaneous placebo or ustekinumab 90 mg subcutaneously every 8 or 12 weeks. The primary endpoint was clinical remission at week 44 (52 weeks after intravenous induction); key secondary endpoints were maintenance of clinical response, endoscopic healing, corticosteroid-free clinical remission, and maintenance of clinical remission among patients who achieved clinical remission at baseline.

Baseline patient characteristics were similar among treatment groups. Significantly greater proportions of ustekinumab-treated patients were in clinical remission at week 44 (43.8% and 38.4%, for patients treated every 8 or 12

Table. Primary and key secondary endpoints [1]

	Placebo (n=175)	Ustekinumab 90 mg q12w (n=172)	Ustekinumab 90 mg q8w (n=176)
Patients in clinical remission at week 44[a]	42 (24.0%)	66 (38.4%); P=0.002	77 (43.8%); P<0.001
Patients maintained clinical response through week 44[b]	78 (44.6%)	117 (68.0%); P<0.001	125 (71.0%); P<0.001
Patients achieved endoscopic healing at week 44[c]	50 (28.6%)	75 (43.6%); P=0.002	90 (51.1%); P<0.001
Patients in clinical remission and not receiving corticosteroids at week 44[a]	41 (23.4%)	65 (37.8%); P=0.002	74 (42.0%); P<0.001
Patients who maintained clinical remission through week 44 among patients in remission at maintenance baselinec	17/45 (37.8%)	26/40 (65.0%); P=0.011	22/38 (57.9%); P=0.069

[a]Mayo score ≤2 points, with no individual subscore >1; [b]Decrease from induction baseline in Mayo score by ≥30% and ≥3 points, with either a rectal bleeding subscore ≤1 or a decrease from induction baseline in rectal bleeding subscore ≥1; [c]Endoscopic improvement in the appearance of mucosa, defined as Mayo endoscopy subscore ≤1

weeks, respectively) compared with placebo (24.0%; P<0.001 and P=0.002, respectively). Also, significantly greater proportions of ustekinumab-treated patients maintained clinical response through week 44 and achieved endoscopic healing and corticosteroid-free clinical remission versus patients on placebo (see Table). Clinical remission through week 44 was maintained for a significantly greater proportion of patients treated every 12 weeks and a numerically greater proportion of patients treated every 8 weeks, compared with placebo-treated patients.

The proportions of patients with all adverse events, infections, and serious infections in the ustekinumab groups were comparable to the placebo group. The proportions of patients who discontinued study agent were lower with ustekinumab than placebo.

1. Danese S et al. UEG Week 2019, Abstract LB07.

Global burden of digestive diseases reveals alarming trends

The results of a major study across 195 countries, presented in a series of late-breaking talks, indicate that global death rates for pancreatic cancer and incidence rates for colorectal cancer both increased by 10% between 1990 and 2017, and that there is an 84% increase in inflammatory bowel disease (IBD) [1-5].

The Global Burden of Disease study is the first comprehensive worldwide estimation of the burden, epidemiological features, and risk factors of several digestive diseases. Some of the key findings were that the number of pancreatic cancer cases increased by 130% over the 27-year study period, from 195,000 in 1990 to 448,000 in 2017. Also, notably, gastric cancer dropped from being the second leading cause of cancer death worldwide to the third position, behind both lung and colorectal cancer. However, on a worrisome note, the number of cases of IBD increased by 84%, from 3.7 million in 1990 to 6.8 million in 2017.

Pancreatic cancer cases rose, which was not surprising; most experts believe this increase is attributable to a rise in the prevalence of obesity and diabetes, two of the leading risk factors for pancreatic cancer. However, the data indicates that pancreatic cancer patients were more likely to survive in 1990 than they are today. Although some of this increased mortality can be explained by the growing population and improved longevity; after normalising for population changes, age-standardised incidence, and death rates, pancreatic cancer-related deaths increased by 10% in this time period. Of note, the highest incidence and death rates were found in higher-income countries.

From 1990 to 2017, age-standardised incidence rates for colorectal cancer increased 9.5% globally but, by contrast, age-standardised death rates decreased by 13.5%. The researchers believe that this is due to the introduction of colorectal cancer screening programmes, leading to earlier detection and an increased chance of survival. Similarly, in countries where screening programmes were established 2 or 3 decades ago, reductions in death rates were observed, supporting the benefits attributable to screening interventions.

The study also indicated that the risk factors for colorectal cancer are different in males and females, which should therefore be considered in national policy and prevention programmes. Alcohol use, smoking, and diets low in calcium, milk, and fibre had a considerable burden on males. For females, dietary risks, but not alcohol use or smoking, were found to be the most attributable risks.

Age-standardised incidence and death rates for gastric cancer decreased steadily between 1990 and 2017. However, this decline has not necessarily led to a lower burden on the health system in high-risk countries and experts believe that specific local strategies should be tailored to each country's risk factor profile. The results were collectively reported in The Lancet Gastroenterology & Hepatology [6].

1. Alatab S et al. UEG Week 2019, Abstract LB22
2. Kamangar F et al. UEG Week 2019, Abstract LB23.
3. Etemadi A et al. UEG Week 2019, Abstract LB24.
4. Pourshams A et al. UEG Week 2019, Abstract LB25.
5. Safiri S et al. UEG Week 2019, Abstract LB2.
6. GBD 2017 Inflammatory Bowel Disease Collaborators. Lancet Gastroenterol Hepatol. 2020 Jan;5(1):17-30.

First evidence of long-term efficacy of ABX464 in ulcerative colitis

Prof. Severine Vermeire (University Hospital Leuven, Belgium) presented a 1-year, open-label ABX464 maintenance study conducted in 22 ulcerative colitis (UC) patients without treatment interruption after completion of the randomised, double-blind, placebo-controlled 8 weeks induction study [1]. A total of 19 patients completed the 1-year maintenance study and showed good long-term safety and tolerability of 50 mg given orally over 52 weeks.

ABX464 is an oral drug candidate for UC, among other chronic inflammation disorders, with a novel mechanism of action based on the upregulation of a single microRNA (miRNA-124) with anti-inflammatory properties.

At month 12 of the maintenance study, an endoscopy to assess clinical remission status (the critical parameter for regulatory authorities) was performed in 16/19 UC patients. During treatment with ABX464, patients reduced their mean total Mayo Score from 8.7 to 1.9 (-78%), their endoscopic subscore from 2.3 to 0.25 (-89%), and their median faecal calprotectin biomarker from 1,044 µg/g to 27.9 µg/g (-97%).

Detailed analysis showed that of the 7/19 patients in clinical remission at the end of the 2-month induction study, 5 were still in clinical remission at the end of the maintenance study (the other 2 patients had missing endoscopy data and could therefore not be assessed). Of the 12/19 patients who were not in clinical remission at the end of the induction study, 7 patients (58%) achieved clinical remission at the end of the maintenance study, while 4 patients had no remission, and 1 had missing endoscopy data. All 3 patients without endoscopy at 12 months had faecal calprotectin levels in the normal range (<50 µg/g), which is indicative of an absence of intestinal inflammation. All 16 patients with endoscopy showed an endoscopic subscore of 0 or 1, indicative of mucosal healing, and in total 12/16 (75%) of the patients undergoing endoscopy achieved clinical remission. The efficacy data from this early study makes ABX464 a very attractive candidate for further development. Furthermore, the data showed that ABX464 maintained the overexpression of miRNA-124 during the 12-month study period.

1. Vermeire S et al. UEG Week 2019, Abstract LB06.

New treatment may reverse coeliac disease

A phase 2a clinical trial demonstrated the proof-of-principle that it is possible to induce immune tolerance to gluten in individuals with coeliac disease. After treatment with investigational drug CNP-101, patients were able to eat gluten with a substantial reduction in inflammation.

Prof. Ciarán Kelly (Harvard Medical School, USA) presented the initial results from the randomised, double-blind, placebo-controlled phase 2a trial which tested CNP-101 8 mg/kg versus placebo in 34 adult coeliac disease patients, assessing the markers of potential efficacy and safety [1]. At inclusion, patients had well-controlled, biopsy-proven coeliac disease and after inclusion they underwent an oral gluten challenge. Treatments were administered intravenously on day 1 and day 8. The gluten challenge began 7 days after the second treatment administration and included 12 grams of gluten per day for 3 days followed by 6 grams of gluten per day for 11 days. The primary endpoint was change from baseline in interferon-gamma (IFN-γ) spot-forming units (SFUs) at day 6 after gluten challenge using a gliadin-specific enzyme-linked immunospot assay. This test is a direct measure of gluten-specific systemic T-cell activation in coeliac disease.

The trial met its endpoint when 28 of the patients completed the 14-day gluten challenge protocol, with a mean change from baseline in IFN-γ immunospot assay of 2.10 with CNP-101 and 17.57 with placebo (P=0.0056). Also seen was a trend in protection from small intestinal mucosal damage with deterioration, although not statistically significant. Mean reduction from baseline in villus height to crypt depth ratio was 0.18 with CNP-101 and 0.63 with placebo (P=0.079). Mean change from baseline in intraepithelial lymphocytes was 28.6 with CNP-101 and 35.0 with placebo (P=0.289).

The most frequent adverse events in patients receiving CNP-101 that exceeded the frequency seen in placebo-treated patients were nausea, headache, abdominal pain, and back pain. In total, 6 patients discontinued due to gluten-related symptoms. No patient had clinically significant changes in vital signs, routine clinical labs, or serum cytokines/chemokines, gliadin-specific T-cell proliferation, and cytokine secretion. Prof. Kelly pointed out that this is the first clinical trial to demonstrate non-autologous induction of antigen-specific immune tolerance in any autoimmune disease.

1. Kelly C et al. UEG Week 2019, Abstract LB18.

IBD prevalence 3 times higher than estimated and expected to rise

New research presented by Dr Dominic King (University of Birmingham, United Kingdom) indicated that the number of people suffering from inflammatory bowel diseases (IBD) is 3 times higher than previous estimates, with sufferers also at a higher risk of developing colorectal cancer [1].

Examining IBD cases from the beginning of the century, the investigators wanted to attain accurate data on ulcerative colitis and Crohn's disease prevalence in the UK. Utilising

data from the Health Improvement Network (THIN), a nationally representative UK primary care database, this new evidence demonstrates that IBD prevalence is 3 times higher than previously reported, with ulcerative colitis and Crohn's disease prevalence increasing by 55% and 83%, respectively, between 2000 and 2017. The study also showed that IBD prevalence is predicted to still rise by almost 25% from 2017 to 2025. "Our study suggests that IBD prevalence is likely to rise substantially over the next decade. As there is currently no known cure for IBD, patients will often need complex and costly treatments throughout their lives. This predicted rise in prevalence may place an even greater strain on already overburdened healthcare systems," Dr King commented.

"The burden of IBD is compounded further by an association with colorectal cancer", he stated. "Our study found that patients suffering from Crohn's disease had a 23% increased risk of developing colorectal cancer compared to matched controls, whilst ulcerative colitis patients had a significantly elevated risk of 43%. The rise in prevalence of IBD could therefore potentially lead to an associated rise in colorectal cancer cases."

1. King D et al. UEG Week 2019, Abstract OP059.

Microbiome and Microbiota

Early stages of gastric metaplasia: molecular profiling

Gastric cancer precursors initiate as a clonal patch, expand by natural drift, and are characterised by a private set of somatic mutations.

Dr William Waddingham (University College London, United Kingdom) started by stating that intestinal metaplasia (IM) can be easily identified by histopathological identification of goblet cells and expression of markers such as CDX2. However, he warned, "the gap in our understanding of the pre-tumour progression is substantial" [1].

Even though the infection rate of *H. pylori* is extensive, the rate of progression, even at advance stages of chronic gastritis, is less than 1 in 200 per year. The current study aimed to answer three questions: (1) How is gastric IM initiated?; (2) How do metaplastic foci spread and expand?; and (3) What are the molecular differences between patches of IM (diversity)? To address these questions, the researchers developed a technique of harvesting a strip of submucosal tissue along the greater curvature of the stomach from distal to proximal and embedding the tissue *en face*, to recreate the birds-eye view of the endoscopist. This technique was performed on tissue from cancer patients (n=16) and samples from patients undergoing bariatric surgery as non-cancer controls (n=16).

The researchers noted that there is a patchwork of foci of precursor lesions. In the control stomachs, there were individual glands of IM evident from histopathological analysis. Using serial thin sectioning of individual metaplastic glands and staining for CDX2, the researchers could identify that IM initiates from a single stem cell and is therefore clonal in nature. To explore the expansion of the IM, the researchers scanned for glands where only part of the gland is characterised by IM, and using quantitative pathology, they calculated how the IM expands and contracts. This result was balanced around 0, to determine if the IM was outcompeting healthy neighbouring parenchyma; in other words, metaplasia reaches fixation by chance, and is natural drift. Quantifying the size of the IM patches was used as a surrogate for clonal expansion. Plotting these data using CDX2 versus cytochrome C oxidase (as a neutral control marker), the researchers concluded that IM displays increased clonal fitness and that inflammation is a primary constraint of clonal expansion.

Thirdly, using laser-capture microdissection of IM clones, the researchers performed whole exome sequencing to capture DNA mutations and copy-number changes, and to reconstruct phylogenetic trees. Each patch had a number of private somatic mutations, confirming their clonal origin, and confirming that a large number of mutations occur prior to

becoming cancer, calculated about 2-3 mutations per year per patient. Each patch shares very few mutations with their neighbour; each is genetically distinct. There was also an increase in copy-number changes in the metaplastic tissue compared with healthy surrounding tissue. Some preliminary work in the epigenetic changes associated with metaplastic tissue suggests that there are broader similarities between patches at the epigenetic level, which drive the phenotypic changes. For example, almost all of the IM patches showed increased methylation at the promoter of the *CDX2* gene.

In summary, intestinal metaplasia in the stomach is derived from a single cell, and each IM patch is genetically distinct, although there may be some epigenetic overlap. Clonal diversity may identify individuals at higher risk for gastric cancer. This study supports the combination of high imaging endoscopy with quantification of the clonal density within a stomach, followed by targeted therapeutic approach based on molecular risk profiling.

1. Waddingham W et al. UEG Week 2019, Abstract OP002.

Plant-based foods and Mediterranean diet associated with healthy gut microbiome

Dietician Laura Bolte (University Medical Center Groningen, the Netherlands) reported findings that certain foods such as legumes, bread, fish, nuts, and wine are associated with high levels of favourable gut bacteria which can aid the biosynthesis of essential nutrients and the production of short-chain fatty acids (SCFAs), the main source of energy for cells lining the colon [1].

The investigators analysed stool samples provided by 1,423 participants in 4 separate study groups: the general population, patients with Crohn's disease, patients with ulcerative colitis, and those with irritable bowel syndrome (IBS). The host's microbiota was analysed and compared with the results of a food frequency survey. The results identified 61 individual food items associated with microbial populations and 49 correlations between food patterns and microbial groups.

The reported findings support the idea that diet could be an effective management strategy for intestinal diseases, through the modulation of gut bacteria. Briefly, it was demonstrated that dietary patterns rich in bread, legumes, fish, and nuts, were associated with a decrease in potentially harmful, aerobic bacteria. Higher consumption of these foods was also associated with lower levels of inflammatory markers in stool that are known to rise during intestinal inflammation. In contrast, a higher intake of meat, fast foods, or refined sugar was associated with a decrease in beneficial bacterial functions and an increase in inflammatory markers. Red wine, legumes, vegetables, fruit, cereals, fish, and nuts were associated with a higher abundance of bacteria with anti-inflammatory functions. Plant-based diets were found to be associated with high levels of bacterial SCFA production, the main source of energy for cells lining the colon. Furthermore, plant protein was found to help the biosynthesis of vitamins and amino acids as well as the breaking down of sugar alcohols and ammonium excretion. In conclusion, animal-derived and plant-derived protein showed opposite associations on the gut microbiota.

Commenting, lead researcher Bolte said, "We looked in depth at the association between dietary patterns or individual foods and gut microbiota. Connecting the diet to the gut microbiome gives us more insight into the relation between diet and intestinal disease. The results indicate that diet is likely to become a significant and serious line of treatment or disease management for diseases of the gut - by modulating the gut microbiome".

1. Bolte L et al. UEG Week 2019, Abstract OP052.

Half of common medications wreak havoc on gut microbiome

A new study by researchers at the University Medical Center Groningen and the Maastricht University Medical Center (the Netherlands) has found that 18 commonly used drug categories extensively affect the taxonomic diversity and metabolic potential of the gut microbiome [1]. Eight different categories of drugs were also found to increase antimicrobial resistance mechanisms in the study participants.

The investigators looked at 41 commonly used drug categories and assessed 1,883 faecal samples from a population-based healthy cohort, patients with inflammatory bowel disease (IBD), and patients with irritable bowel syndrome (IBS) intermixed with healthy controls. The researchers compared the profiles based on taxonomic characteristics and metabolic functions of medication users to non-medication users, looking at the effect of single medication use and then combined medication use.

Among the drug categories, the researchers found that those with the biggest impact on the microbiome include proton pump inhibitors (PPIs), which are taken by >11% of the European population. PPIs are used to treat dyspepsia, peptic ulcers, in the eradication of *H. pylori*, gastro-reflux, as well as Barrett's oesophagus. Similarly, metformin, commonly used as a treatment for Type 2 diabetes, affected the gut microbiome significantly. Not surprisingly, antibiotics, taken by 34% of the European population each year, made it to the top modulator drug categories. Finally, laxatives also restructured the taxonomy and metabolism of the gut microbiome. Notable findings were that the gut microbiota of PPI users showed increased abundance of upper gastrointestinal tract bacteria and increased fatty acid production, while metformin users had higher levels of the potentially harmful bacteria *E. coli*.

The researchers also found that an additional 7 drug categories were associated with significant changes in bacterial populations in the gut. SSRI-antidepressant use in patients with IBS was associated with excessive levels of the potentially harmful bacteria species *Eubacterium ramulus*. The use of oral steroids was associated with high levels of methanogenic bacteria which has been associated with weight gain and obesity.

The authors concluded that the changes observed as a result of common medication use likely increase the risk of intestinal infections, obesity, and other serious conditions and disorders linked to the gut microbiome in the general population, with specific risks being increased in patients with a digestive disorder such as IBD or IBS.

1. Vich Vila A et al. UEG Week 2019, Abstract OP334.

Antibiotic resistance in *H. pylori* has doubled over last 20 years

New research presented by Prof. Francis Megraud (University of Bordeaux, France) focused on antibiotic resistance in *H. pylori* and found that the rate of primary clarithromycin resistance has doubled in the last 20 years [1].

A total of 18 countries participated in the study. Resistance was highest in Southern Italy (approximately 40%), Croatia, and Greece (35% and 30% respectively). This was presumably attributable to the overuse of antibiotics for common viral infections; and aggravated by the lack of cooperation by medical institutions when it comes to limiting the use of antibiotics. These findings support data that both Italy and Greece have the highest mortality rates for antibiotic resistance among EU member countries. Comparable rates of antibiotic resistance were found in Poland, Bulgaria, Ireland, Austria, France, and Germany. Nations with the lowest rates of resistance include Denmark, at just 5%, Latvia, with about 7%, and Norway and the Netherlands, at about 9% each.

If *H. pylori* infection is not controlled due to rising antibiotic resistance rates, gastric cancer rates are likely to increase in conjunction with increasing rates of gastric ulcer. Explaining the situation, Prof. Megraud said, "With resistance rates to commonly used antibiotics such as clarithromycin increasing at an alarming rate of nearly 1% per year, treatment options for *H. pylori* will become progressively limited and ineffective if novel treatment strategies remain undeveloped."

1. Megraud, F et al. UEG Week 2019, Abstract OP035.

Pancreatitis

New model predicts recurrence of acute biliary pancreatitis

Prof. Daniel de la Iglesia-Garcia (University Hospital of Santiago de Compostela, Spain) presented a new scoring model to predict recurrence from a multicentre, retrospective cohort study of patients with a first episode of acute biliary pancreatitis (ABP) [1].

Clinical guidelines for acute pancreatitis (AP) recommend cholecystectomy during the index admission of patients with ABP. This recommendation is not consistently followed, and as a result, the risk of recurrence of ABP is increased. Prof. de la Iglesia-Garcia said that his team aimed to develop a model to determine the risk of recurrence of ABP to prioritise patients on surgical waiting lists. The study made use of a multicentre,

Table. RABP scoring system to stratify patients with acute biliary pancreatitis into low (4 to 8 points), intermediate (9 to 11 points), or high-risk groups (12 to 13 points) [1]

Level of Alkaline Phosphatase	Points
0 to 263 (Normal limit)	5
264 to 526 (2 ULN)	4
527 to 789 (3 ULN)	3
790 to 1,052 (4 ULN)	2
> 1,052	0
Severity of acute pancreatitis	
Mild acute pancreatitis	4
Moderate acute pancreatitis	2
Severe acute pancreatitis	0
ERCP	
No	4
Yes	0

retrospective cohort study of patients with a first episode of ABP from January 2010 to December 2015 (n=498). Patients were included upon abdominal ultrasound identification of stones or sludge/microlithiasis in the common bile duct or gallbladder (identified on endoscopic ultrasonography or magnetic resonance cholangiography), together with the absence of AP relapse after cholecystectomy. The primary outcome was the risk of ABP recurrence during the 6-month period after the first episode.

Median time to cholecystectomy was 136 days (range 72-206 days). Patients waiting more than 6 months for cholecystectomy were excluded. A total of 352 patients were finally included (mean age 67.6 years, range 51.6 -77.4; 199 female). ABP relapse occurred in 89 patients (25.3%). Serum alkaline phosphatase at admission, previous endoscopic sphincterotomy, and the severity of the first episode of ABP were all significantly associated with ABP recurrence. The investigators developed a score system (recurrence acute biliary pancreatitis -RABP- score, see Table) based on these measures to categorise patients with ABP into low-, intermediate-, or high-risk groups of recurrence. Assigned scores identified patients with ABP who recurred with a c-statistic of 0.59 (95% CI 0.55-0.64; P<0.01). In the future, this score might be applied to prioritise patients in surgical waiting list for cholecystectomy.

1. de la Iglesia-Garcia D et al. UEG Week 2019, Abstract OP304

Interim data on GOULASH-PLUS trial

Dr Dorottya Kato (University of Pécs, Hungary) presented the 14-month follow-up data in the GOULASH-PLUS trial, which indicated 19% recurrence of acute pancreatitis (AP) and 45.3% of patients who displayed some level of carbohydrate metabolism disorder [1].

Recurrent AP (RAP) develops in 20% of patients and chronic pancreatitis (CP) occurs in 7%–12.8%. However, there is not sufficient information to establish an evidence-based statement to define early CP, or how to prevent its development.

The reported study is an observational prospective follow-up study of the GOULASH-trial in which (1) patients with all severities of pancreatitis were included; (2) patients received only therapeutic modalities which are accepted by the evidence-based medicine (EBM) guideline; (3) whole blood, serum, and plasma samples were collected; and (4) patient-related variables including anamnestic data, physical examination, laboratory parameters, imaging, therapy, and complications were collected. The aim of GOULASH-PLUS study is to understand the influencing factors of CP and to determine which parameters should be measured to detect the early phase of CP.

In total, 93 of the 126 included patients (73.8%) received a first-year check-up within the trial. Their mean age was 54 years and 61.2% was male. Mild, moderate, and severe AP was observed in 69 (74%), 19 (21%), and 5 (5%) patients during their index admission. About 20% of patients (18/126) was admitted with recurrent AP. At the first-year follow-up, 9 patients were newly diagnosed with diabetes, and 21 patients had impaired glucose tolerance. The incidence of diabetes increased after the first year of AP from 12.9% to 22.7%, and at 12 months follow-up 45.3% of the patients had evidence of glucose intolerance. Patients who were admitted with moderate or severe AP were more likely to develop diabetes (5/24 patients; 20.8%) than patients with mild AP (4/69 patients; 5.8%).

1. Kato D et al. UEG Week 2019, Abstract OP305.

Hepatology

Restrictive strategy for cholecystectomy selection does not reduce pain, but does reduce surgery

Usual care for symptomatic patients with gallstones is suboptimal and patients often suffer pain after surgery. The SECURE study demonstrated that a restrictive patient selection strategy, where only patients with specific gallstone-related symptoms undergo surgery, did not result in more pain-free patients but did reduce the number of surgeries being performed.

Prof. Joost Drenth (Radboud University Medical Center, Nijmegen, the Netherlands) started by pointing out that although laparoscopic cholecystectomy for the treatment of symptomatic cholecystolithiasis is currently the standard of care, persistent post-cholecystectomy pain occurs in 10–41% of patients [1]. The aim of the SECURE study was to compare the non-inferiority of a restrictive strategy with stepwise selection with usual care, to assess (in)efficient use of cholecystectomy in a multicentre, randomised, parallel-arm, non-inferiority study in 24 academic and non-academic hospitals in the Netherlands. The primary endpoint, powered for non-inferiority, was the proportion of patients who were pain-free at 12-month follow-up, analysed by intention-to-treat and per protocol. A 5% non-inferiority margin was chosen, based on the estimated difference that would be clinically relevant in practice. Safety analyses were also done in the intention-to treat population.

The investigators enrolled 1,067 patients aged 18–95 years with abdominal pain and gallstones or sludge identified by ultrasound. Patients were randomly assigned (1:1) to either usual care in which selection for cholecystectomy was left to the discretion of the surgeon or a restrictive strategy with stepwise selection for cholecystectomy. For the restrictive strategy, cholecystectomy was advised for patients who fulfilled 5 pre-specified criteria: (1) severe pain attacks, (2) pain lasting 15–30 min or longer, (3) pain located in epigastrium or right upper quadrant, (4) pain radiating to the back, and (5) a positive pain response to simple analgesics. Randomisation was stratified for centre (academic vs non-academic and patient volume), gender, and body-mass index.

At baseline, patients in the restrictive strategy group reported more severe pain attacks than patients in the usual care group (83% vs 77%, respectively; P=0.008), and more patients fulfilled all 5 pre-specified restrictive strategy criteria in the restrictive strategy group than in the usual care group (38% vs 28%, respectively; P=0.001). At 12-month follow-up, 298 patients (56%; 95% CI 52.0–60.4) were pain-free in the restrictive strategy group, compared with 321 patients (60%; 95% CI 55.6–63.8) in usual care. Non-inferiority was not shown (difference 3.6%; one-sided 95% lower CI −8·6%; Pnon-inferiority=0.316). According to a secondary endpoint analysis, the restrictive strategy resulted in significantly fewer cholecystectomies than usual care (68% vs 75%; P=0.01).

There were no between-group differences in trial-related gallstone complications (8% in usual care vs 7% in restrictive strategy; P=0.16) and surgical complications (21% vs 22%, respectively; P=0.77), or in non-trial-related serious adverse events (5% in both groups).

This study was limited by the higher proportion of patients reporting severe pain at baseline in the restrictive strategy group, and the fact that some patients in the restrictive strategy group underwent cholecystectomy despite failing to satisfy the cholecystectomy selection criteria. In summary, this study illustrates that current treatment of symptomatic gallstone disease is not improved by a restrictive strategy.

1. Drenth J et al. UEG Week 2019, Abstract IP233.

β-blockers may halt cirrhosis progression: PREDESCI trial

In patients with compensated cirrhosis and portal hypertension, β-blocker use reduced decompensation risk but not mortality.

Prof. Candid Villaneuva (Hospital Creu Sant Pau, Barcelona, Spain) presented the PREDESCI trial, a randomised, double-blind, placebo-controlled trial which aimed to determine whether reducing portal pressure with β-blockers lowers decompensation and death rates in 201 patients (of the 631 patients evaluated) with compensated cirrhosis and

clinically significant portal hypertension (CSPH) defined by a hepatic venous pressure gradient ≥10 mmHg) without high-risk varices [1].

Participants were split into 2 groups based on their response to β-blockers: a β-blocker–responsive group, defined as ≥10% drop in hepatic venous pressure gradient from baseline when given a propranolol infusion challenge (n=135) or a β-blocker–nonresponsive group (n=66). The responsive group was then randomised to receive either propranolol or placebo and the nonresponsive group to either carvedilol or placebo. The primary endpoint was incidence of decompensation or death.

During a median follow-up of 37 months, among the 100 patients who received β-blockers, the rate of decompensation or death was significantly lower compared with the 101 patients who received placebo (16% vs 27%; HR 0.51; 95% CI 0.26-0.97; P=0.04). This difference was attributable to a significantly lower incidence of ascites (HR 0.44; 95% CI 0.20–0.97; P=0.03). Rates of encephalopathy, haemorrhage, and mortality were similar between groups.

In conclusion, this study suggests that in patients with compensated cirrhosis and CSPH, long-term treatment with non-selective β-blockers halves the risk of decompensation or death. Importantly, these results suggest that patients with compensated cirrhosis should be screened for CSPH, and started on a non-selective β-blocker if it is present.

1. Villanueva C et al. UEG Week 2019, Abstract IP235.

Obeticholic acid prevents liver fibrosis from NASH

Obeticholic acid (OCA) 25 mg significantly improved fibrosis and key components of disease activity among patients with non-alcoholic steatohepatitis (NASH). The results from this planned interim analysis show clinically significant histological improvement that is reasonably likely to predict clinical benefit.

Dr Isabel Graupera (Institut d'Investigacions Biomediques August Pi I Sunyer, Barcelona, Spain) reported the positive results from the prespecified 18-month interim analysis of the phase 3, randomised, double-blind, placebo-controlled, multicentre study REGENERATE study of OCA in patients with liver fibrosis due to NASH [1], which was conducted to assess the effect of OCA on liver histology comparing baseline biopsies with biopsies taken at month 18. The intention-to-treat population for the interim analysis included 931 patients with stage 2 and 3 fibrosis (placebo, n=311; OCA 10 mg, n=312; OCA 25 mg, n=308). REGENERATE has completed target enrolment for the clinical outcomes cohort, with 2,480 adult NASH patients randomised, and will continue through clinical outcomes for verification and description of clinical benefit.

The fibrosis improvement endpoint was achieved by 37 (12%) patients in the placebo group, 55 (18%) in the OCA 10 mg group (P=0.045), and 71 (23%) in the OCA 25 mg group (P=0.0002). The NASH resolution endpoint was not met (8% of patients in the placebo group, 11% in the OCA 10 mg group [P=0.18], and 12% in the OCA 25 mg group [P=0.13])

The safety population of the interim analysis included 1,968 randomised patients who received at least one dose of study drug (OCA or placebo). Adverse events were generally mild to moderate in severity and the most common were consistent with the known profile of OCA. The frequency of serious adverse events was similar across treatment arms (11% in placebo, 11% in OCA 10 mg, and 14% in OCA 25 mg). The most common adverse event reported was dose-dependent pruritus (placebo, 19%; OCA 10 mg, 28%; OCA 25 mg, 51%). The large majority of pruritus events were mild to moderate. Dr Graupera concluded, "The antifibrotic efficacy observed with just 18 months of OCA treatment in REGENERATE is particularly meaningful because fibrosis is the most important histological predictor of liver failure and death in patients with NASH."

1. Graupera I et al. UEG Week 2019, Abstract OP196.

Oncology

Metal stents are better than plastic for endoscopic biliary drainage

In the Netherlands, biliary drainage with self-expanding metal stents (SEMS) is insufficiently implemented; patients drained with a SEMS had a reduced rate of cholangitis and clinically relevant postoperative pancreatic fistula.

In pancreatic ductal adenocarcinoma, patients are recommended by European guidelines to undergo endoscopic biliary drainage (EBD) with SEMS. Dr Anouk Latenstein (Amsterdam University Medical Center, the Netherlands) presented a study which aimed to assess the implementation of SEMS use in daily clinical practice in patients with resectable pancreatic head cancer undergoing EBD [1]. The study also aimed to define the link between SEMS, drainage-related complications, and post-operative complications. The researchers performed a nationwide, retrospective cohort study including 585 patients (mean age 68) with pancreatic ductal adenocarcinoma who underwent EBD prior to pancreatoduodenectomy in the mandatory Dutch Pancreatic Cancer Audit (January 2017 - December 2018). Drainage-related complications were pancreatitis, cholangitis, perforation, bleeding, and occlusion. Post-operative complications were post-operative pancreatic fistula, delayed gastric emptying, post-pancreatectomy haemorrhage, bile leakage, lymphatic leakage, pneumonia, and wound infection.

EBD was mostly performed with plastic stents (n=331, 57%) rather than SEMS (n=254, 43%). Drainage-related complications were comparable between patients with SEMS (18%) and plastic stents (19%). Cholangitis occurred less often in patients with SEMS compared with plastic stents (5% vs 11%; P=0.029). Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis occurred in 9% and 8% in patients with SEMS and plastic stents, respectively. In multivariable logistic regression, adjusted for patient characteristics, SEMS was associated with lower odds of cholangitis (OR 0.394; 95% CI 0.176-0.881). Post-operative pancreatic fistula occurred less often in patients with SEMS compared with plastic stents (10% vs 19%; P=0.011) and this effect remained after adjustment for patient characteristics in multivariable logistic regression (OR 0.568; 95% CI 0.324-0.995).

The study underscored that despite explicit European guideline recommendations, biliary drainage with SEMS placement is insufficiently implemented in the Netherlands. Patients drained with a SEMS had a reduced rate of cholangitis and clinically relevant post-operative pancreatic fistula. In conclusion, clinical thinking stipulates that surgery should be first in patients with obstructive jaundice [2], based on the DROP-study. However, if that is not possible, then the patient should be moved to ERCP and stenting, and in that case SEMS is the preferred option.

1. Latenstein A et al. UEG Week 2019, OP038.
2. van der Gaag NA, et al. N Engl J Med. 2010 Jan 14;362(2):129-37.

Ramosetron relieves low anterior resection syndrome

Prof. Kyu Joo Park (Seoul National University Hospital, Korea) reported a randomised controlled trial to assess the effectiveness of ramosetron, a serotonin (5-hydroxytryptamine [5-HT]3) receptor antagonist, for the treatment of anterior resection syndrome. Ramosetron significantly improved both the Low Anterior Resection Syndrome (LARS) score, as well as quality of life [1].

5-HT3 receptor antagonists are effective for the treatment of irritable bowel syndrome, in which exaggerated intestinal/colonic hypermotility is observed. Recent studies have suggested that the motility disorder, especially spastic hypermotility, seen in the neorectum following sphincter-preserving operations for rectal cancer may be the basis of the post-operative defecatory malfunction seen in in 60-90% of patients, and for whom there are no effective treatments.

The investigators wished to investigate whether 5-HT3 receptor antagonist ramosetron could be effective in male patients suffering from severe low anterior resection syndrome after rectal cancer surgery. Enrolled patients were randomly allocated to an arm taking ramosetron 5 mg daily

(n=48) or to conservative treatment (n=50) for 1 month. The LARS questionnaire determined the LARS score at the study start and after 1 month after treatment [2], which was the primary endpoint of the study. The secondary endpoint was the difference of patients' quality of life as assessed by the of EORTC QLQ-C30 questionnaire. Patient characteristics did not differ between arms regarding tumour distance from the anal verge, stage of the tumour, stool frequency, or mean LARS score at start of study.

After 1 month, the LARS score significantly decreased from 36.0 ± 5.9 to 29.6 ± 9.3 in the ramosetron group (P<0.001) and it was significantly lower in the ramosetron group than in the control group (29.6 ± 9.3 vs 34.6 ± 7.6; P=0.004). The mean change in LARS score (1 month - baseline) was also significantly different (-6.48 in ramosetron vs 0.16 in the control group; P<0.001). The proportion of severe LARS (LARS score ≥30) after 1 month was 58.3% (n=28/48) in the ramosetron group vs 82.0% (n=41/50) in the control group (P=0.011). The stool frequency after 1 month was 7.1/day vs 10.5/day in the ramosetron and control group, respectively (P=0.004). Patients with <4 stools/day were 13 (27.1%) in the ramosetron group vs 1 (2.0%) in the control group (P<0.001). Furthermore, the quality of life after 1 month was significantly better in ramosetron group in terms of general health status, physical functioning, emotional functioning, and cognitive functioning.

1. Park KJ et al. UEG Week 2019, Abstract OP241.
2. Emmertsen KJ, Laurberg S. Ann Surg 2012;255:922-8.

Immunonutrition during neoadjuvant oesophagogastric cancer therapy: no benefit

Immunonutrition is enteral or total parenteral nutrition feeding enriched with various pharmaconutrients (arginine, glutamine, omega-3-fatty acids, nucleotides, and anti-oxidants: copper, selenium, zinc, vitamins B, C, and E) to improve immune responses and modulate inflammatory responses. Prof. Sheraz Markar (Imperial College London, United Kingdom) presented a large, multicentre, blinded clinical trial, which did not demonstrate any major benefit for patients taking immunonutrition during neoadjuvant therapy in patients with oesophageal or gastric cancer [1].

Malnutrition in oesophagogastric cancers is associated with poor outcomes including decreased quality of life (QoL). The aim of this double-blinded, randomised controlled, multicentre clinical trial was to evaluate whether immunonutrition during neoadjuvant treatment prior to surgery would improve patients' QoL, and reduce postoperative morbidity. Adult patients with untreated non-metastatic upper GI tumours were randomised to receive immunonutrition (n=148) or an isocaloric control (n=152) during neoadjuvant therapy. The primary endpoint for the study was QoL, as measured by the EORTC-QLQ-C30. Secondary endpoints included diarrhoea, mucositis, haematologic toxicity, nutritional status, compliance and response to neoadjuvant therapy, postoperative morbidity, and length of hospital stay.

There were no significant differences between the groups at diagnosis vs 30 days postoperatively, either in global health score (HR 1.18; 95% CI 0.843-1.652; P=0.112), time to global health deterioration (P=0.527), physical functioning (P=0.976), role functioning (P=0.777), emotional functioning (P=0.545), cognitive functioning (P=0.207), social functioning (P=0.968), or fatigue score (P=0.920). In addition, no improvements were noted in pain severity, nausea and vomiting, dyspnoea, insomnia, appetite loss, or stool frequency. However, the single 30-day postoperative improvement was the duration of pain and discomfort in patients taking immunonutrition (P=0.007).

Thus, this large, multicentre trial did not demonstrate any major benefit for patients taking immunonutrition during neoadjuvant therapy in patients with oesophageal or gastric cancer, beyond a shortened duration of discomfort.

1. Markar S et al. UEG Week 2019, Abstract OP239.

Endoscopy

EUS-guided histological specimens from the pancreatic cyst wall

Prof. Borjan Kovacevic (University Hospital Copenhagen, Denmark) showed that obtaining endoscopic ultrasound (EUS)-guided histological specimens from the pancreatic cyst wall was feasible across clinics, although it might be a procedure best reserved for selected patients [1].

EUS-guided histological specimens from the pancreatic cyst wall can be obtained through a through-the-needle microbiopsy forceps, although the value of this instrument has not yet been tested in a multicentre clinical setting. In the presented study, patients referred for EUS evaluation of pancreatic cysts in whom EUS-guided microbiopsy was attempted (n=28) were included from 6 tertiary centres.

The technical success rate was 85.7% (n=24). Biopsies were generally of good quality and contributed to the diagnosis in 20 patients (clinical success of 71.4%). Only 3 adverse events were recorded (10.7%). Technical failure seems to be caused by loss of flexibility of the echoendoscope when both forceps and the FNA needle are inserted. Other technical difficulties described did not hinder procurement of the specimens. Failures were seen in locations where EUS-guided puncture is known to be challenging (i.e. when the echoendoscope was placed in the duodenum). The majority of the procedures was performed using a flexible nitinol needle (n=18/28), but no firm conclusions can be drawn on the potential role of needle flexibility in the ability to obtain biopsy samples with the microbiopsy forceps. Even though no severe or fatal adverse events were recorded, a rate of 10.7% is notable and should be interpreted with caution due to the limited number of patients.

It was concluded that the use of the microbiopsy forceps is feasible with acceptable rates of technical and clinical success across centres. However, the occurrence of adverse events may preclude routine incorporation of this method, and it may be most appropriate to apply only to patients with uncertain cystic lesions where surgery is considered, as these might benefit from this form of extended diagnostics. Prospective studies are warranted to determine the diagnostic potential compared with other modalities.

1. Kovacevic B, et al. UEG Week 2019, Abstract LB10.

Digital single-operator cholangioscopy more sensitive than endoscopic retrograde cholangiopancreatography

Dr Christian Gerges (Evangelisches Krankenhaus, Düsseldorf, Germany) presented a prospective, multi-centre, randomised controlled, post-market study showing that digital single-operator cholangioscopy (DSOC)-guided biopsies are safe and effective with a higher sensitivity compared with standard endoscopic retrograde cholangiopancreatography (ERCP) techniques in the visual and histopathological diagnosis of indeterminate biliary strictures [1].

Indeterminate biliary strictures remain a challenge to accurately diagnose, because they cannot be distinguished as malignant or benign despite initial ERCP and standard sampling methods. Biopsy under direct cholangioscopic vision might be superior to standard ERCP techniques such as brushing or biopsy. The aim of this study was to investigate whether DSOC improves the diagnostic yield in patients with indeterminate biliary strictures, compared with standard ERCP work-up. The primary endpoint was diagnostic accuracy of cholangioscopy or cholangiography at 6 months after the initial ERCP procedure. A total of 61 patients were determined to have an indeterminate biliary stricture based on magnetic resonance cholangiopancreaticography (MRCP) in 3 tertiary referral centres. They were randomised to standard ERCP visualisation with tissue brushing (Control

Table. Diagnostic accuracy of ERCP brushing versus DSOC biopsy on first sample [1]

Lesion based on ERCP brushing	Final diagnosis		Lesion based on DSOC biopsy	Final diagnosis	
	Malignant	Benign		Malignant	Benign
Malignant	3	0	Malignant	15	0
Benign	6	11	Benign	6	5
Intermediate	5	2	Intermediate	1	3

	ERCP brushing	DSOC biopsy	P-value
Sensitivity	3/14 (21.4%)	15/22 (68.2%)	≤0.01
Specificity	11/13 (84.6%)	5/8 (62.5%)	0.25
Positive predictive value	3/3 (100%)	15/15 (100%)	0.99
Negative predictive value	11/17 (64.7%)	5/11 (45.5%)	0.31
Overall accuracy	14/27 (51.9%)	20/30 (66.7%)	0.25

arm) or DSOC visualisation and DSOC-guided biopsy (Study arm). The pathologist was procedure-blinded. Patients in the Control arm underwent an ERCP with cholangiography. A cholangiography-based impression of malignancy (yes/no/indeterminate) was recorded. ERCP-guided brushing was performed with a minimum of 9 passes. Malignancy was determined by cytology or histology on tissue sampling during the index or subsequent ERCP procedure, or surgical specimen histopathology up to 6 months after the index procedure. The assessed stricture was considered benign if malignancy was not confirmed by 6 months after the index procedure. Diagnostic accuracy of only the first procedure was compared between the groups.

The first sample sensitivity of DSOC-guided biopsies was significantly higher than ERCP-guided brushing (68.2% vs 21.4%; P<0.01; see Table). The sensitivity of visualisation (Study arm, 95.5% vs Control arm, 66.7%; P=0.02) and overall accuracy (Study arm, 87.1% vs Control arm, 65.5%; P=0.05) were significantly higher in the Study arm compared with the Control arm, whereas no significant differences were found in specificity, positive predictive value, or negative predictive value. Adverse events were equally low in both arms.

In conclusion, DSOC-guided biopsies are safe and effective with a higher sensitivity compared with standard endoscopic retrograde cholangiopancreatography ERCP techniques for indeterminant biliary strictures.

1. Gerges C et al. UEG Week 2019, Abstract LB11.

New single-use duodenoscope well-liked by endoscopists

Expert endoscopists reported good overall performance of a new single-use duodenoscope in an initial case series of patients scheduled for endoscopic retrograde cholangiopancreatography (ERCP).

Dr Andrew Ross (Virginia Mason Medical Center, Washington, USA) presented the study which aimed to assess overall satisfaction of the performance of new EXALT single-use Model D disposable duodenoscope in a series of human cases [1]. Because inadequate reprocessing of reusable duodenoscopes can lead to infection transmission, a new single-use duodenoscope was recently developed (see Figure).

Figure. The new EXALT single-use Model D disposable duodenoscope.

It had comparable performance to reusable duodenoscopes when tested by expert endoscopists in a comparative bench model for ERCP. In total, 60 consecutive adult patients in 6 academic medical centres had an ERCP using the first-generation single-use duodenoscope in April and May 2019. Seven ERCP experts rated the new EXALT single-use Model D duodenoscope in ERCP procedures for overall satisfaction on a scale of 1 (unsatisfied) to 10 (very satisfied); preference (Not preferred/Neutral/Preferred) compared with reusable duodenoscopes on 23 ERCP manoeuvres; and qualitative comparison of 17 performance characteristics on a scale of 1 to 5 (again, compared with reusable duodenoscopes). All 60 ERCP procedures were successfully performed, 58 (96.7%) with the single-use duodenoscope alone and 2 (3.3%) with crossover to a reusable duodenoscope.

Median overall satisfaction with the single-use duodenoscope was rated 9.0 (range 1-10). The overall satisfaction rating was ≥7 in 56 (93.3%) ERCPs. All three ratings were at or above midpoint (overall satisfaction ≥5, comparative ERCP manoeuvre "Neutral/Preferred", and qualitative comparative rating of performance characteristic ≥3 in 47 (78.3%) cases. Low (≤4) overall satisfaction ratings in 4 ERCPs were attributed to suboptimal positioning of the duodenoscope in front of the papilla; these ERCPs were a subset in which biliary or pancreatic duct strictures were dilated and/or stented.

The investigators concluded that the 7 endoscopists in this study were highly satisfied with the single-use duodenoscope in ERCP procedures.

1. Ross A et al. UEG Week 2019, Abstract LB12.