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Introduction FGF19 is a polypeptide hormone produced in the ileum which inhibits hepatic synthesis of bile acid and is thought to have roles in regulation of bile acid pool size and in clinical conditions of diarrhoea. Fasting serum levels of FGF19 are reduced in patients with Crohn's disease (CD) involving the ileum and also in patients with CD and ileal resections (IR). Aims: To investigate the relationship between serum FGF19 and disease activity in CD and length of ileal resection.
Methods Blood samples were taken prospectively from patients after an overnight fast in 40 patients with Crohn's disease (24 non resected and 16 with previous IR), 19 healthy controls and 75 disease controls with SeHCAT negative chronic idiopathic diarrhoea. In 9 IR patients clinical records were available to establish the precise length of ileum resected. Disease activity was assessed by Harvey-Bradshaw Index (HBI). Diarrhoea was defined as stool frequency ≥3, Bristol stool chart ≥6. Serum FGF19 was measured by ELISA and data are expressed as medians and ranges. Nonparametric statistical tests (Mann–Whitney and Spearman rank correlations) were used.
Results Median levels of FGF19 were significantly lower in patients with non-resected CD (114 pg/ml, 3–339) compared to healthy controls (231 pg/ml, 74–655, p=0.002 and 0.005 respectively). Patients with previous IR (71 pg/ml, 17–152) had significantly lower levels than non-resected CD (p=0.02). Out of 15 patients with non resected CD with ileal or ileo-colonic disease, eight had active disease (HBI>4) and had further radiological or endoscopic assessment of the ileum: four with symptomatic strictures had significantly higher FGF19 levels (328 pg/ml, 178–339) compared to the inactive patients (118 pg/ml, 46–256, p=0.04). Conversely, four with non-obstructive ileal inflammation had significantly lower FGF19 levels (33 pg/ml, 3–59) than inactive patients (p=0.01) and this group had the lowest observed levels of FGF19. Six non resected CD with diarrhoea had significantly lower levels of FGF19 (86 pg/ml, 30–169) compared to the diarrhoea controls (246 pg/ml, 72–1000, p=<0.0001). In nine IR patients an inverse correlation between FGF19 levels and resection length was observed (r=−0.81, p 0.01).
Conclusion Fasting serum levels of FGF19 are significantly reduced by IR or non obstructive ileal inflammation. Symptoms of diarrhoea in CD are associated with low levels of FGF19 and an inverse correlation is found between FGF19 and the length of previous ileal resections.

Competing interests None declared.

OC-081 GENETIC POLYMORPHISMS AND PATTERNS OF FGF19 RESPONSE TO MEALS IN PRIMARY BILE ACID DIARRHOEA

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Introduction Primary bile acid diarrhoea (PBAD) is associated with low median serum fibroblast growth factor 19 (FGF19) levels. Our group has suggested that PBAD results from impaired negative feedback by FGF19 on the enzyme CYP7A1, leading to over production of bile acids, which spill over into the colon leading to diarrhoea. We aim to characterise abnormalities in FGF19 in PBAD, in particular the response of the hormone to meal stimuli and to describe phenotypic patterns of response. We have explored possible associations of genetic polymorphisms with both PBAD and specific phenotypes.
Methods Subjects with PBAD were prospectively recruited. After an overnight fast, blood was sampled every 90 min for 6 h. Meals were provided at 9:00 and 12:00. Serum FGF19 was quantified by ELISA using a commercially available kit. Three phenotypes of meal stimulated FGF19 response are described: 1. Low-low (L-L) all five serum FGF19 levels <400 pg/ml. 2. Low-high (L-H) sample 1 400 pg/ml sample 4 or 5 >400 pg/ml. 3. High-high (H-H) samples 1 and 3 or 5 >300 pg/ml. In a separate part of the study genomic DNA was extracted from 91 subjects with PBAD and 120 diarrhoea control subjects. Eight SNPs were analysed, two from the FXR gene (rs61755050, rs56163822), two from the FGF19 gene (rs1789170, rs948992) as well as SNPs from the genes for OSTα, klothoβ, FGFR4 and ASBT (rs939885, rs17618244, rs376618, rs188096). Genotyping was performed using Taqman SNP genotyping assays.
Results 18 subjects underwent serial FGF19 sampling. Seven were defined as L-L response, five as L-H and four as H-H. Two subjects did not match criteria for the subtypes. The seven L-L subjects had lower SeHCATs compared with L-H and H-H combined (p<0.05). Five subjects had SeHCATs of <5%, all but one were L-L. Overall, subjects with lower SeHCATs had lower FGF19 levels. Area under the curve was lower for those with SeHCAT <5% than those above (median 701 pg/ml h vs 1655 pg/ml h p=0.023). The FGF19 level at 1.5 h correlated with subjects' SeHCAT (r=0.49, p=0.04). The ASBT SNP was associated with L-L subjects, present in four out of seven (p<0.05). No other significant SNP associations were found within the phenotypes described nor between PBAD as a whole and diarrhoea controls.
Conclusion Serial FGF19 sampling in PBAD identified three responses to meal stimulus. Most individuals with severe PBAD have L-L response of FGF19, and most of these have a polymorphism in the gene for ASBT. L-H and H-H phenotypes are seen in those with higher SeHCATs. The L-H pattern resembles that previously reported in healthy individuals. These patterns may represent a defect in the receptor component of the feedback mechanism for BA synthesis.

Competing interests None declared.

OC-082 26-WEEK EFFICACY AND SAFETY OF ONCE-DAILY ORAL LINACLOTIDE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME WITH CONSTIPATION (IBS-C): A EUROPEAN PERSPECTIVE

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Introduction Linaclotide, a minimally absorbed guanylate cyclase-C receptor agonist, is an investigational drug treatment for IBS-C. As part of the European Medicines Authority submission we evaluated the efficacy and safety of linaclotide 290 μg, administered once daily for 26 weeks (wks), in a Phase 3 trial of patients with IBS-C.
Methods In a randomised, double-blind, Phase 3 trial, IBS-C patients (modified Rome II criteria) with an overall complete spontaneous bowel movement (CSBM) frequency of <3/wk, an overall spontaneous bowel movement (SBM) frequency of ≤5/wk and an average abdominal pain score of ≥3 (0–10 scale) during a 2 wk baseline period were randomised to linaclotide or placebo for 26 wks of treatment. Efficacy parameters were analysed at 12 and 26 wks.
Results In total, 804 patients (female 90%; median age 44 years) received linaclotide (n=401) or placebo (n=403). During the 2 wk baseline period, 87% had abdominal pain every day (mean score 5.6;

0–10 scale) and 76% had no CSBMs (mean rate 0.2/wk). Significant improvements in linaclotide-treated patients were seen for both co-primary and all 12 secondary parameters. For the first co-primary parameter (≥30% reduction from baseline in mean abdominal pain or discomfort score with neither score worsening for ≥6 of the first 12 wks), 54.1% of linaclotide-treated patients and 38.5% of placebo-treated patients were responders (p<0.0001). For the second co-primary parameter ("considerably relieved" or "completely relieved" on the weekly degree-of-relief of IBS symptoms question for ≥6 of the first 12 wks), 39.4% of linaclotide-treated patients and 16.6% of placebo-treated patients were responders (p<0.0001). Similar improvements in both co-primary endpoints were seen at 26 wks (53.6% vs 36.0%, 37.2% vs 16.9%; both p<0.0001). Also, rates for sustained abdominal pain/discomfort response and sustained IBS degree-of-relief response at 12 and 26 wks were significantly greater in linaclotide-treated vs placebo-treated patients (all p<0.0001). Linaclotide significantly improved CSBMs, stool consistency, straining, bloating, SBMs, abdominal pain and abdominal discomfort vs placebo over 12 and 26 wks (p<0.0001). The most common adverse event (AE) was diarrhoea, causing discontinuation in 4.0% of linaclotide-treated and 0.2% of placebo-treated patients.

Conclusion Treatment of IBS-C with linaclotide produced statistically significant improvements in abdominal and bowel symptoms at 12 wks and were sustained over 26 wks. Diarrhoea was the most common AE.

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OC-083 OPTIMISING RADIATION BOWEL INJURY THERAPY, THE ORBIT STUDY, A RANDOMISED CONTROLLED TRIAL

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Introduction Chronic gastrointestinal (GI) symptoms after radical pelvic radiotherapy are common. There is no evidence whether medical intervention helps. Most affected patients are never referred to specialists. We developed a comprehensive, peer-reviewed management algorithm for patients with new onset GI symptoms after pelvic radiotherapy. A prospective three arm randomised controlled trial was performed to test two hypotheses: (1) intervention using our algorithm provides benefit at 6 months after randomisation compared to no intervention; (2) outcomes do not differ when patients are managed by nurse or doctor. Other end points include: cost-effectiveness of intervention; effect on non-GI symptoms; outcomes after 12 months.

Methods Consenting people who had completed pelvic radiotherapy >6 months previously with persisting GI symptoms were randomised to see a GI nurse or gastroenterologist, both following our algorithm, or to receive the MacMillan booklet "Pelvic radiotherapy: possible late effects". After 6 months patients in the booklet arm with persisting symptoms could see the gastroenterologist. Patients in the nurse arm, were transferred to the gastroenterologist if they had problems beyond the algorithm's scope. The primary end point was change in the modified Inflammatory Bowel Disease Questionnaire-bowel sub score (IBDQ-B). The trial was designed with 80% power to answer the 1st hypothesis after randomising 196 patients and the 2nd after closing the booklet arm, and randomising 22 more patients to gastroenterologist or nurse.

Results This 1st analysis includes 152 men, 44 women randomised to the three arms and followed for 6 months: booklet (n=68) vs combined treatment arms (66 nurse, 62 gastroenterologist). Median age was similar in both groups (69 years range 29–87); 25 patients had radiotherapy for GI, 30 gynaecological, 141 urological cancer. 18 (9%) withdrew/were withdrawn from the trial; 26 (38%) from the booklet group and 5 (8%) from the nurse arm crossed to the gastroenterologist. Intention to treat analysis showed a non-significant (p=0.056) improvement in IBDQ-B score of 2.8 points (95% CI 6.5 to −0.1). Planned per protocol analysis in 158 patients with complete data sets showed significant (p=0.041) improvement in IBDQ-B between treated and non-treated arms of 3.4 points (95% CIs 6.7 to 0.1).

Conclusion Medical intervention can ameliorate radiotherapy-induced GI symptoms. A 2nd analysis in December 2012 will address the other end points and the 2nd hypothesis. This study was funded by RFPB, NIHR.

Competing interests None declared.

Oesophageal free papers

OC-084 THE CLONAL PROGRESSION OF BARRETT'S OESOPHAGUS TO OESOPHAGEAL ADENOCARCINOMA

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Introduction Barrett's oesophagus (BO) is a common premalignant condition, wherein the normal squamous oesophageal epithelium is replaced by a columnar, intestinal phenotype. It is the predominant risk factor for the development of oesophageal adenocarcinoma (OA)[1] which develops through a metaplasia: dysplasia: carcinoma sequence. Initial studies suggested that BO lesions were genetically clonal.[2] However; our group has shown, by gland micro-dissection, that multiple clones are present within BO and it is therefore a genetically heterotypic disease.[3] Furthermore, Maley *et al*[4] have shown that genetic diversity increases the risk of BO progressing to cancer. Here, we demonstrate that although Barrett's dysplasia is polyclonal, oesophageal adenocarcinomas arising from Barrett's are typically clonal.

Methods DNA was macro-dissected from dysplastic and cancerous regions of endoscopic mucosal resection (EMR) and oesophagectomy specimens and screened for mutations in p16*INK4A*, *TP53* and *K-RAS*. Mutated specimens were serially sectioned; crypts and carcinomas were histologically graded and then micro-dissected using a P.A.L.M. laser capture microscope. DNA was extracted from dissected material and was sequenced for the point mutations identified in the initial screen.

Results Individual glands from 10 specimens (EMRs and oesophagectomies) were laser captured and sequenced for mutations identified as per above. Seven specimens contained *TP53* mutations and the three remaining specimens were mutated for p16*INK4A*.