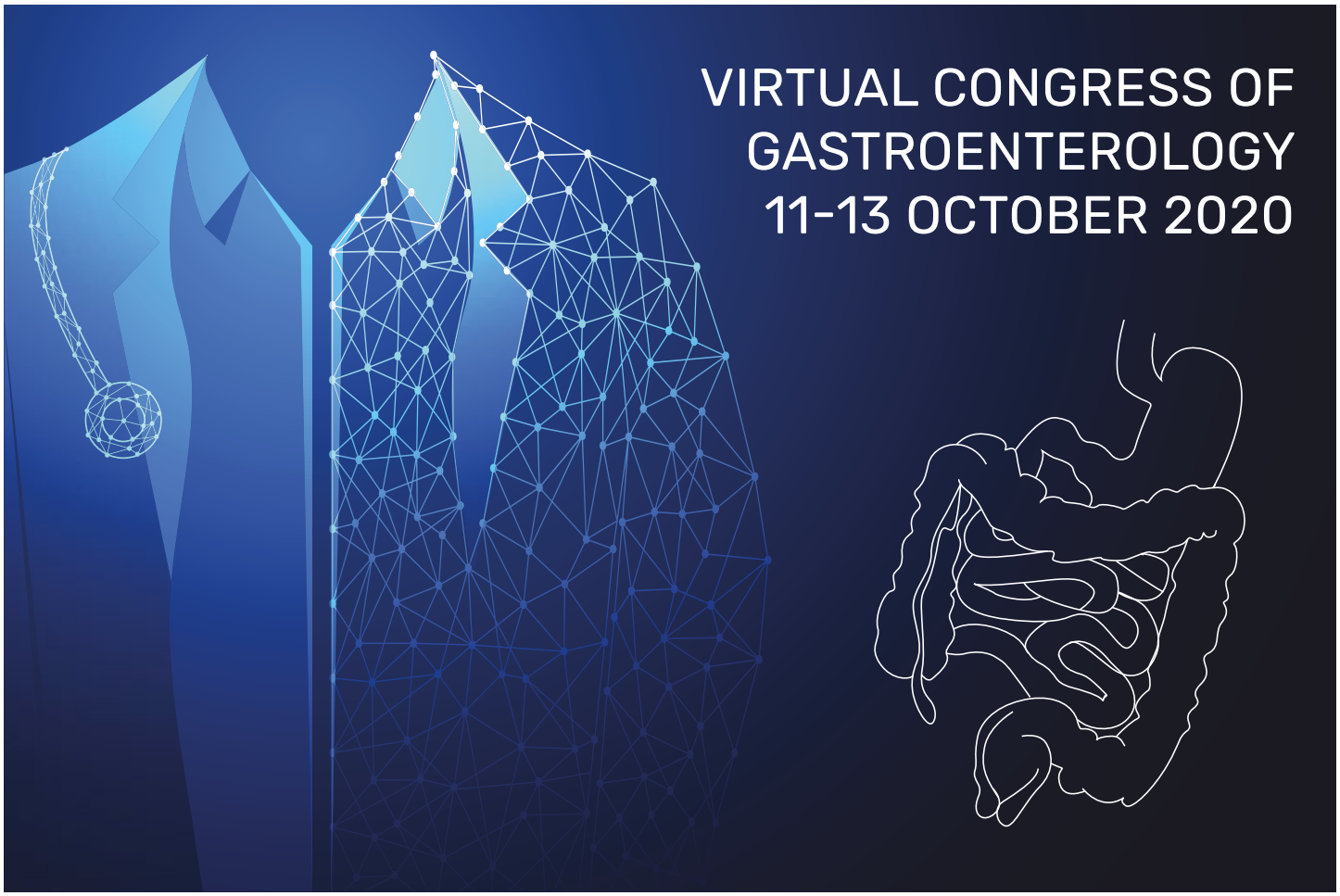
United European Gastroenterology Week (UEGW)



Content

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"Listen to the UEGW 2020 Virtual Meeting – Highlights"

Summary of articles presented at the UEGW 2020 Virtual Meeting:

- Sustained efficacy of mirikizumab in moderate-to-severe Crohn's disease.
- Risk factors for severe COVID-19 among IBD patients.
- Sustained response to faecal microbiota transplantation.
- Plecanatide effective for IBS with constipation
- Dupilumab improves in diverse aspects of eosinophilic oesophagitis

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1. Sustained efficacy of mirikizumab in moderate-to-severe Crohn's disease

Mirikizumab demonstrated sustained efficacy at week 52 in patients with moderate-to-severe Crohn's disease. During the maintenance period of the phase 2 SERENITY trial, few patients discontinued due to adverse events [1].

Mirikizumab, a monoclonal antibody targeting the p19 subunit of IL-23, has demonstrated clinical efficacy in phase 2 trials in psoriasis and ulcerative colitis. The phase 2 SERENITY trial showed that mirikizumab was more effective than placebo for inducing clinical and endoscopic remission and response at 12 weeks in patients with moderate-to-severe Crohn's disease. At the UEG Week 2020, results of maintenance treatment at week 52 were presented.

Patients who received mirikizumab and achieved ≥1 point improvement at week 12 in the Simple Endoscopic Score for Crohn's Disease (SES-CD) were re-randomised to continue intravenous (IV) mirikizumab treatment Q4W (IV-C; n=41) or to receive 300 mg subcutaneous (SC) mirikizumab Q4W (SC; n=46).

The primary endpoint (endoscopic response at week 12) has been previously reported [2]. Endoscopic response (50% reduction from baseline in SES-CD) for IV-C versus SC was 56.1% versus 52.2% in week 12, and 58.5% versus 58.7% in week 52. Endoscopic remission rates for IV-C versus SC were 14.6% versus 30.4% in week 12 and 19.5% versus 32.6% in week 52.

Among those with endoscopic response at week 12, 69.6% in the IV-C group and 66.7% in the SC group also had an endoscopic response at week 52. Among those with endoscopic remission at week 12, 50.0% in the IV-C group and 64.3% in the SC group also had endoscopic remission at week 52. Similar frequencies of treatment-emergent adverse events (AEs) and serious AEs were reported in IV-C and SC groups. One patient in each group discontinued due to an AE.

During the maintenance period of SERENITY, mirikizumab demonstrated sustained efficacy at week 52 with few discontinuations due to AEs. These phase 2 data support continued characterisation of mirikizumab efficacy and safety in Crohn's disease in an ongoing phase 3 program, called VIVID.

1. Sands BE. Efficacy and safety of mirikizumab after 52-weeks maintenance treatment in patients with moderate-to-severe Crohn's disease. UEG Week Virtual 2020, abstract OP108.
2. Sandborn WJ, et al. J. Gastroenterol. Feb. 1, 2020:158(3); p537-549.e10.

2. First randomised T2T trial using endoscopy to guide dose escalation

STARDUST is the first randomised treat-to-target (T2T) trial using endoscopy at week 16 to guide dose escalation in patients with Crohn's disease [1]. After 48 weeks maintenance therapy with ustekinumab, a numerically higher proportion of patients achieved an endoscopic response in the T2T versus standard-of-care arm. Hence, T2T could be an additional tool for physicians to guide ustekinumab dosing decisions in Crohn's disease.

T2T has been proposed as an effective strategy to optimise management of Crohn's disease. The phase 3b STARDUST trial compared a T2T maintenance strategy with standard-of-care in 500 patients with active, moderate-to-severe Crohn's disease who failed conventional therapy and/or 1 biologic.

Patients received intravenous, weight-based ustekinumab (~6mg/kg) at week 0 (baseline) and thereafter subcutaneous ustekinumab 90 mg at week 8. At week 16, CDAI 70 responders were randomised 1:1 to the T2T or standard-of-care arm. Patients in the T2T arm were assigned to subcutaneous ustekinumab every 12 or 8 weeks based on 25% improvement in Simple Endoscopic Score in Crohn's disease (SES-CD) score versus baseline.

From week 16-48, ustekinumab dose was increased up to every 4 weeks if the following targets were not met: CDAI <220 and ≥70-point improvement from baseline, and C-reactive protein ≤10mg/L or faecal calprotectin ≤250µg/g.

The current analysis evaluated endoscopic and clinical results after 48 weeks. A numerically higher proportion of patients in the T2T achieved the primary endpoint, namely ≥50% reduction in SES-CD versus baseline, at week 48 compared with the standard-of-care arm: 37.7% versus 29.9% (P=0.0933; non-responder imputation [NRI]). A statistically significant difference was reached in a sensitivity analysis: 40.0% T2T versus 30.8% standard-of-care (P=0.0494; last observation carried forward [LOCF]).

At week 48, high clinical response rates were achieved in both arms:

- T2T 68.2% versus standard-of-care 77.8% (P=0.02; NRI);
- T2T 89.5% versus standard-of-care 89.6% (P>0.05; LOCF).

Furthermore, high biomarker responses were achieved in T2T versus standard-of-care regarding improvement of ≥50% in faecal calprotectin (39.4% versus 46.5% (P>0.05; NRI); and 63.1% versus 60.6% (P>0.05; LOCF)) and C-reactive protein (41.7% versus 53.3% (P=0.032; NRI); and 53.2% versus 57.2% (P>0.05; LOCF)). No new safety signals were reported.

The current results suggest that T2T could be an additional tool for physicians to guide ustekinumab dosing decisions in Crohn's disease.

1. Danese S. Clinical and endoscopic response to treat-to-target versus standard of care in Crohn's disease patients treated with ustekinumab: week 48 results of the STARDUST trial. UEG Week Virtual 2020, abstract LB11.

3. Endoscopy can be delivered safely during the COVID-19 pandemic

High-quality therapeutic endoscopy services can be delivered safely in appropriately prioritised patients during the COVID-19 pandemic [1]. The authors presented their experiences with ERCP, EUS, luminal stenting, and dilatation during this period.

In the UK, the COVID-19 pandemic began in mid-March 2020 and peaked by late April. In the following months, the UK was in an early recovery phase of restarting endoscopy after the first wave of COVID-19. The British Society of Gastroenterology has provided guidance for managing endoscopy services in this period.

The current study aimed to assess the number of COVID-19-positive swabs in the 28 days following a procedure. At the beginning of the pandemic, patients were screened for COVID-19 prior to their endoscopic procedures using a symptom-based questionnaire. From 18 May 2020 onwards, all patients attending therapeutic endoscopic procedures underwent a SARS-CoV-2 nasopharyngeal swab 1-3 days prior to the procedure, in addition to a screening questionnaire for COVID-19 symptoms.

All therapeutic procedures from 18 March –when the pandemic emerged in the UK– until 31 July were included and all patients were followed up for 30 days post procedure. Between 18 March and 17 May, 110 therapeutic procedures were performed, and between 18 May and 31 July 169 procedures were performed.

No swabs were COVID-19-positive in the 28 days after the procedure. Overall, common bile duct (CBD) cannulation was achieved in 90.4% of procedures and 82.2% of ERCP procedures was done on a naïve papilla. CBD cannulation in naïve papilla was 89.2%. Of all ERCP procedures, 47.9% was performed for stone disease (duct clearance rate 88.6%). A total of 91% had a successful stent insertion in biliary stricture disease. Of 91 EUS procedures, 63 were diagnostic and 28 biopsy (diagnostic yield 89%). Nine patients underwent successful oesophageal stenting and 33 patients underwent successful oesophageal dilatation (both 100% technical and clinical success). One patient underwent successful colonic decompression. Procedure-related mortality was 0.7% (2 patients).

This study confirms that in appropriately prioritised patients high-quality therapeutic endoscopy service can be delivered safely during the COVID-19 pandemic.

1. Esmaily S. ERCP, EUS, luminal stenting and dilatation: experience from a university teaching hospital in the United Kingdom during the covid 19 pandemic. UEG Week Virtual 2020, abstract LB03.

4. Risk factors for severe COVID-19 among IBD patients

Increasing age, comorbidities, and corticosteroids are associated with severe COVID-19 among IBD patients, according to a large, international registry created to monitor outcomes of IBD patients with confirmed COVID-19, called SECURE-IBD [1]. Notably, use of TNF antagonists does not appear to be associated with severe COVID-19.

The impact of COVID-19 on patients with inflammatory bowel disease (IBD) is not well characterised. The SECURE-IBD survey catalogued the clinical course of COVID-19 among IBD patients and evaluated the association between demographics, clinical characteristics, and immunosuppressant treatments on COVID-19 outcomes.

Reported were 959 COVID-19 cases from 40 countries (median age 43 years, 52% men). Of those, 86 patients (9%) had severe COVID-19, 320 (33%) were hospitalised, and 37 patients died (3.9% case fatality rate). Age-standardised mortality ratios for IBD patients were:

- 2.0 relative to data from China;
- 1.7 relative to data from Italy; and
- 1.9 relative to data from the US.

Furthermore, the investigators aimed to identify factors associated with severe COVID-19, defined as intensive care unit admission, ventilator use, and/or death, using multivariable logistic regression.

Risk factors found for severe COVID-19 among IBD patients in the current study included:

- increasing age: adjusted odds ratio (aOR) 1.04;
- 1 comorbidity in addition to IBD: aOR 2.60;
- ≥2 comorbidities: aOR 4.8;
- systemic corticosteroids: aOR 5.1; and
- sulfasalazine or 5-aminosalicylate use: aOR 2.0.

In contrast, TNF antagonist treatment was not associated with severe COVID-19 (aOR 0.9).

The SECURE-IBD registry showed an association between increasing age, comorbidities, and corticosteroids and severe COVID-19 among IBD patients. Nevertheless, no association was found for TNF antagonists with severe COVID-19.

1. Ungaro R. Impact of COVID-19 on patients with inflammatory bowel disease: data from an international registry. UEG Week Virtual Symposium 2020, abstract OP153.

5. Post-colonoscopy colorectal cancers in IBD patients

Post-colonoscopy colorectal cancers accounted for a substantial proportion of all IBD-related colorectal cancers. However, IBD patients had an overall low absolute risk of post-colonoscopy colorectal cancers [1].

Post-colonoscopy colorectal cancers are defined as colorectal cancers diagnosed within 6-36 months following a colonoscopy. While post-colonoscopy colorectal cancers account for up to 8% of all colorectal cancers, they could account for up to 50% of all colorectal cancers diagnosed in patients with inflammatory bowel diseases (IBD). However, few studies have investigated the absolute risk in IBD patients undergoing colonoscopy.

In a Danish population-based cohort study, almost 35,000 IBD patients who underwent colonoscopy, 138 post-colonoscopy colorectal cancers were found compared with 1,909 post-colonoscopy colorectal cancers among more than 350,000 non-IBD patients. The 6-36 month cumulative incidence proportion of post-colonoscopy colorectal cancers after first-time colonoscopy was 0.21% for IBD patients and 0.37% for non-IBD patients. The absolute risks were comparably low after subsequent colonoscopies for both IBD and non-IBD patients.

Comparing IBD with non-IBD patients, the hazard ratio (HR) of post-colonoscopy colorectal cancers after the first colonoscopy was 0.96 and the HRs after subsequent colonoscopies were also close to 1.0. The 3-year rate of post-colonoscopy colorectal cancers was 24.3% for IBD patients (19.2% for patients with Crohn's disease and 26.4% for patients with ulcerative colitis) compared with 7.5% for non-IBD patients.

Finally, the investigators calculated 3-year rates of post-colonoscopy colorectal cancers in IBD and non-IBD patients, stratified by the total number of colonoscopies performed during the study period. This rate was found to increase with the total number of colonoscopies performed for both IBD as well as non-IBD patients.

A better understanding of IBD-related post-colonoscopy colorectal cancer risk would improve patient guidance clinical decision-making, and help foster the understanding of post-colonoscopy colorectal cancer development. As demonstrated in the current Danish study, post-colonoscopy colorectal cancers accounted for a substantial proportion of all IBD-related colorectal cancers, nevertheless, the absolute risk was low.

An explanation for the high 3-year rates of post-colonoscopy colorectal cancers is an increased colonoscopy frequency in IBD patients, thereby increasing the likelihood that observed colorectal cancer are categorised as post-colonoscopy colorectal cancers.

1. Troelsen FS. Risk of a post-colonoscopy colorectal cancer diagnosis in patients with inflammatory bowel disease: a Danish population-based cohort study. UEG Week Virtual 2020, abstract OP027.

6. Adenoma detection rate improves over time

Likely due to increased awareness and accumulating experience in detection, an analysis of an Australian tertiary health network showed a significant improvement in overall sessile serrated adenoma detection rate (SSADR) over 4 years. However, a brief educational intervention did not further improve SSADR [1].

The SSADR for colonoscopists is increasingly considered as a quality marker of an effective colonoscopy. As per recent Australian standards, hospitals currently need to monitor the SSADR of their colonoscopists. The Australian Colonoscopy Recertification Program recommends an SSADR of ≥4%. Therefore, educational programmes aiming to improve SSADR are highly relevant.

The current study analysed 1,763 colonoscopies from July 2018-January 2019 (pre-intervention) and 1,843 from March 2019-September 2019 (post-intervention). The overall detection rates were:

- adenoma detection rate (ADR): 40.5% pre-intervention versus 42.4% post-intervention (P=0.25); and
- SSADR: 9.2% pre-intervention versus 9.3% post-intervention (P=0.95).

The overall ADR detection rates pre-intervention and post-intervention for different healthcare professionals were respectively:

- non-interventional gastroenterologists: 34.8% versus 38.8% (P=0.23);
- interventional gastroenterologists: 50.0% versus 48.9% (P=0.82);
- nurse endoscopists: 52.3% versus 53.8% (P=0.79);
- colorectal surgeons: 32.1% versus 33.1% (P=0.76); and
- general surgeons: 26.7% versus 25.5% (P=1).

No differences were found in bowel preparation quality, caecal intubation rate, or indications. Compared with the control cohort of 1,562 colonoscopies between 1 July 2015-31 December 2015, overall baseline SSADR improved significantly: 6.0% versus 9.3% (P<0.05). General surgeons significantly improved both their baseline ADR and SSADR, while colorectal surgeons and nurse endoscopists had a significantly improved baseline ADR.

The overall ADR and SSADR recorded at this Australian health network are well above the recommended detection rates. Overall SSADR improved significantly over 4 years between 2015 and 2019.

A brief educational intervention did not further improve SSADR. This may be because the intervention was too brief to induce behaviour change or because once an adequate benchmark is reached, it is difficult to further enhance detection rates.

1. Nalankilli K. Sessile serrated adenoma/polyp (SSA/P) detection rates have improved over a 4-year period, but have not improved further after a targeted educational intervention at an Australian tertiary health network. UEG Week Virtual Symposium 2020, abstract LB07.

7. Sustained response to faecal microbiota transplantation

Most IBS patients who responded to faecal microbiota transplantation after 3 months maintained this response at 1 year after the intervention. In this study from Norway, the improvements in symptoms and quality of life increased significantly over time [1]. Sustained changes in the faecal bacteriome and consequent short-chain fatty acid metabolites seemed to associate with better clinical outcomes.

A recently published study from Norway showed that faecal microbiota transplantation is an effective and safe treatment for patients with irritable bowel syndrome (IBS) after 3 months [2]. The current follow-up study investigated the efficacy and safety of faecal microbiota transplantation at 1 year after this intervention.

The response to faecal microbiota transplantation was maintained at 1 year after treatment in 86.5% and 87.5% of patients who received 30 g and 60 g faecal microbiota transplantation, respectively. In the 30 g faecal microbiota transplantation group, 21.6% of patients showed complete remission (IBS-Severity Scoring System total score of ≤75) after 3 months, which increased to 32.4% at 1 year. In the group receiving 60 g, the percentage of patients with a complete remission increased from 27.5% after 3 months to 45% at 1 year. Abdominal symptoms, fatigue, and quality of life were also improved at 1 year compared with 3 months after faecal transplantation.

These findings were accompanied by a significant improvement in the dysbiosis index and comprehensive changes in the faecal bacterial profile. The levels of *Alistipes* spp. were significantly lower in the relapsed patients at baseline than in the responders and patients in remission at 1 year after faecal microbiota transplantation. Thus, *Alistipes* spp. seem to play a central role in the improvements seen after faecal transplantation. Levels of *Alistipes* spp. were postulated to be used to predict the outcome of faecal microbiota transplantation.

The reduction of acetic acid levels could be relevant since acetic acid has been found to induce visceral hypersensitivity in rodents.

Changes in the levels of faecal short-chain fatty acids indicated that the microbial metabolism changed from a saccharolytic to a proteolytic fermentation pattern in IBS patients at 1 year after faecal transplantation. The level of faecal acetic acid was reduced compared with baseline. Furthermore, the clinically relapsed patients had significantly lower fatigue scores and significant changes in the bacterial profile and the levels of short-chain fatty acids compared with baseline.

The finding that faecal microbiota transplantation induced remission in about half of the patients with IBS emphasises the role of the intestinal microbiota in the aetiology of IBS.

1. El-Salhy M. Long-term effects of faecal microbiota transplantation (FMT) in patients with irritable bowel syndrome. UEG Week Virtual Symposium 2020, abstract OP059.
2. El-Salhy M, et al. Gut. 2020 May;69(5):859-867.

8. Plecanatide effective for IBS with constipation

The uroguanylin analogue plecanatide is an effective symptomatic treatment for patients with irritable bowel syndrome with constipation (IBS-C) [1]. An early clinical response to plecanatide appeared to be predictive of overall response after a treatment duration of 12 weeks.

Plecanatide is indicated for the treatment of adults with IBS-C or chronic idiopathic constipation. In two phase 3 trials (NCT02387359 and NCT02493452), the efficacy and safety of plecanatide were demonstrated in patients with IBS-C. The current pooled analysis of these trials evaluated whether the treatment response during week 2 or 4 was predictive of overall treatment response after 12 weeks in 2,176 patients with IBS-C.

At baseline, complete spontaneous bowel movements per week were present in mean 0.25 of patients. The mean number of spontaneous bowel movements per week was 1.46. At baseline, patients had moderately severe abdominal pain (mean severity score of 6.25). The percentage of responders increased from week 2 to week 4:

- from 11.9% to 16.2% in the placebo group;
- from 20.7% to 24.2% of patients who received plecanatide 3 mg; and
- from 20.1% to 24.3% of patients who received plecanatide 6 mg.

Across weeks 1-12, significantly more plecanatide-treated patients were overall responders compared with the placebo group:

- 16.0% in the placebo group;
- 25.6% in the plecanatide 3 mg group (P<0.001 vs placebo); and
- 26.7% in the plecanatide 6 mg group (P< 0.001 vs placebo).

Being a weekly responder during either week 2 or 4 was significantly predictive of overall-responder status during weeks 1-12.

Patients experiencing a response at week 2 were 29.5 times more likely to be overall responders than those who did not experience a response at week 2 (P<0.001). Furthermore, patients with a response in week 4 were 61.3 times more likely to be overall responders than those who did not experience a response in week 4 (P<0.001). Similar results were found in patients with a sustained response (overall responders who were weekly responders for ≥2 of the last 4 weeks).

Plecanatide, both dosed at 3 mg and 6 mg, was found to be an effective symptomatic treatment for IBS-C. A clinical response to plecanatide as early as week 2 appeared to be predictive of overall response after 12 weeks of treatment.

1. Quigley EM. Early response to plecanatide predicts overall and sustained efficacy in patients with irritable bowel syndrome with constipation. UEG Week Virtual 2020, abstract OP057.

9. Dupilumab improves in diverse aspects of eosinophilic oesophagitis

Weekly dupilumab demonstrated significant and clinically meaningful improvements in histologic, symptomatic, endoscopic, and molecular aspects of eosinophilic oesophagitis (EoE). In addition, dupilumab was well tolerated. That was found in part A of an ongoing 3-part, randomised, placebo-controlled, phase 3 study [1].

EoE is a chronic type 2 inflammatory disease of the oesophagus that can substantially impair the quality of life. Only a few treatment options are currently available and the response to the current therapy is generally suboptimal.

Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13. These cytokines are key drivers of type 2 inflammation in EoE. In a previous phase 2 proof-of-concept study, dupilumab significantly improved histological and clinical outcomes of EoE with an acceptable safety profile. In the current, ongoing, phase 3 trial, the efficacy and safety of weekly dupilumab 300 mg are compared with placebo in 81 adult and adolescent patients with EoE with a treatment duration of 24 weeks.

The first primary endpoint was the proportion of patients achieving a peak oesophageal intraepithelial eosinophil count of ≤6 eosinophils per high-power field. At week 24, a significantly higher proportion of patients treated with dupilumab versus placebo achieved:

- a peak eosinophil count of ≤6 eosinophils per high-power field: 59.5% versus 5.1% (P<0.001); and
- a peak eosinophil count of <15 eosinophils per high-power field: 64.3% versus 7.7% (P<0.001).

Furthermore, dupilumab-treated versus placebo-treated patients had a significantly greater percent change from baseline in:

- peak eosinophil count: LS mean difference -68.26 (P<0.001);
- Dysphagia Symptom Questionnaire score: LS mean difference -12.32 (P<0.001); and
- total EoE Endoscopic Reference Score: LS mean difference -2.9 (P<0.001).

Dupilumab was generally well tolerated with an acceptable safety profile. The most common treatment-emergent adverse events for dupilumab versus placebo were injection-site reactions (16.7% vs 10.3%) and nasopharyngitis (11.9% vs 10.3%).

1. Dellon ES. Dupilumab efficacy and safety in adult and adolescent patients with eosinophilic esophagitis: results from part A of a randomized, placebo-controlled three-part, phase 3 study. UEG Week Virtual Symposium 2020, abstract LB22.

10. Possible causal link between eosinophilic inflammation and anxiety

After a 10-year follow-up, anxiety at baseline was independently associated with a 15-fold increased risk of eosinophilia, while anxiety at follow-up was associated with a 5-fold increased risk with duodenal eosinophilia [1]. A prospective population-based study from Sweden demonstrated for the first time a possible causal link between duodenal inflammation and psychological distress in a functional gut disorder.

Functional dyspepsia is a distressing, frequent disorder with a prevalence of approximately 15% in the general population. Anxiety was found to be strongly associated with new-onset functional dyspepsia. In addition, increased duodenal eosinophil counts have been observed in patients with functional dyspepsia. Gut symptoms may precede the development of anxiety in patients with a functional gut disorder. However, the underlying mechanisms are unknown. Duodenal eosinophilia is a potential cause of anxiety.

Population-based study from Sweden

From the national Swedish population register, 3,000 people were randomly selected. Subsequently, the participants were surveyed by the validated Abdominal Symptom Questionnaire (ASQ) and the Hospital Anxiety and Depression Scale (HADS). An oesophagogastroduodenoscopy was performed in 1,000 participants. All persons who were eligible from the latter cohort (n=887, response rate 79%), were invited to a follow-up with the ASQ and HADS. Functional dyspepsia was defined based on the Rome III. Anxiety and depression were defined by a score of ≥11 on the HADS.

In a nested case-control study, 89 patients with functional dyspepsia were compared with 124 healthy controls (mean age 62 years, 34% male). Duodenal histology was evaluated at baseline and divided into 2 groups, based on a pre-specified cut-off for the eosinophil count in the duodenal bulb:

- D1: cut-off of 23 eosinophils; and
- D2: cut-off of 24 eosinophils in the second part.

Duodenal eosinophilia and anxiety

Duodenal eosinophilia was observed in 78 subjects in D1 and 84 subjects in D2 (in 46 subjects, both in D1 and in D2, P<0.001 for both) at baseline. Anxiety at baseline was found in 9 subjects (4%) and at follow-up in 12 subjects (6%).

After adjustment for age, gender, and functional dyspepsia status at baseline, the following associations between anxiety and duodenal eosinophilia were observed:

- Anxiety at baseline was independently associated with duodenal eosinophilia in D2 (P=0.013, OR=15.0), but not in D1 (P=0.2).
- Anxiety at follow-up was independently associated with duodenal eosinophilia in D1 at baseline (P=0.025, OR=5.90), but not D2 (P=0.5).
- Anxiety at follow-up was independently associated with functional dyspepsia at baseline (P=0.004, OR=7.42).

New-onset anxiety was more common in individuals meeting criteria for eosinophilia in D1 (7.5%) than those who did not meet the criteria (1.8%). The association was strong (OR=4.48), but failed to reach statistical significance (P=0.08). Hence, duodenal eosinophilia may be one mechanism by which anxiety arises in functional dyspepsia.

1. Ronkainen J. Inter-relationships of duodenal eosinophilia, anxiety and functional dyspepsia. UEG Week Virtual Symposium 2020, abstract OP158.

11. Filgotinib effective as maintenance treatment for ulcerative colitis

The phase 2b/3 SELECTION study found that the JAK1 inhibitor filgotinib was effective and well tolerated as maintenance treatment for patients with moderately- to severely-active ulcerative colitis who had achieved clinical response to induction treatment with this drug [1].

Filgotinib is being investigated for several inflammatory conditions, including ulcerative colitis. The SELECTION maintenance study evaluated maintenance treatment with filgotinib in 664 patients with moderately- to severely-active ulcerative colitis who achieved clinical remission or Mayo Clinic Score (MCS) response after 10 weeks of induction with filgotinib 100 mg or 200 mg or placebo. Approximately 40% of patients were biologic-experienced. Patients randomised to filgotinib induction were re-randomised to their induction filgotinib dose or placebo. Patients randomised to placebo during induction continued placebo maintenance. Mandatory steroid tapering was required.

The primary endpoint was endoscopic/rectal bleeding/stool frequency (EBS) remission at week 58, defined by Mayo endoscopic subscore ≤1, rectal bleeding subscore=0, and ≥1-point decrease in stool frequency subscore (SFS) from baseline and SFS ≤1. A significantly higher proportion of patients on filgotinib achieved EBS remission compared with placebo:

- 11.2% with placebo versus 37.2% with filgotinib 200 mg; and
- 13.5% with placebo versus 23.8% with filgotinib 100 mg.

In addition, significantly higher proportions of patients achieved key secondary endpoints, including 6-month corticosteroid-free clinical remission and histologic remission, with filgotinib 200 mg versus placebo:

- 6-month corticosteroid-free clinical remission: 5.1% with placebo versus 27.2% with filgotinib 200 mg;
- sustained clinical remission: 9.2% with placebo versus 18.1% with filgotinib 200 mg;
- MCS remission: 6.1% with placebo versus 34.7% with filgotinib 200 mg; and
- endoscopic remission: 13.3% with placebo versus 15.6% with filgotinib 200 mg.

Overall, the incidences of adverse events (AEs), serious AEs, and discontinuations due to AEs were similar across treatment arms. Serious infections and herpes zoster infections were infrequent across groups, and no opportunistic infections occurred. There were no venous thromboses, including pulmonary embolism, among filgotinib-treated patients.

The current analysis of the SELECTION study showed that filgotinib was effective as maintenance treatment for patients with moderately- to severely-active ulcerative colitis who had achieved clinical response to induction treatment with filgotinib. Moreover, filgotinib 200 mg met all key secondary endpoints including endoscopic, histologic, and 6-month corticosteroid-free remission.

1. Peyrin-Biroulet L. Efficacy and safety of filgotinib as maintenance therapy for patients with moderately to severely active ulcerative colitis: results from the phase 2B/3 SELECTION study. UEG Week Virtual Symposium 2020, abstract LB20.

12. No improvements of remission with etrolizumab in ulcerative colitis

Etrolizumab, an anti-β7 monoclonal antibody, inhibits both trafficking of immune cells into the gut and their inflammatory effects on the gut lining. Results from the LAUREL trial showed that despite nominally significant benefits with etrolizumab compared with placebo in endoscopic improvement, endoscopic remission, and histologic remission at week 62 among week 10-responders was not met in a cohort of TNF-naïve ulcerative colitis patients [1].

The phase 3 LAUREL trial evaluated the safety, efficacy, and tolerability of etrolizumab in 359 patients with moderately- to severely-active ulcerative colitis who were naïve to TNF antagonists. In the induction phase, patients received subcutaneous, open-label etrolizumab. The induction phase to week 10 was completed by 347 participants, of whom 214 clinical responders were randomly assigned at week 12 to etrolizumab or placebo, administered every 4 weeks for a total of 52 weeks in the maintenance phase. At week 62, 74.1% of etrolizumab patients and 39.6% of placebo patients had completed the maintenance phase.

The primary efficacy endpoint was remission, defined as a Mayo Clinic total score ≤2 with individual subscores ≤1 and a rectal bleeding subscore of 0, at week 62 among patients with a clinical response, defined as a Mayo Clinic total score with a ≥3-point decrease and 30% reduction from baseline and ≥1-point decrease in rectal bleeding subscore or a score of 0 or 1, at week 10.

At week 62, the remission rate observed in patients assigned to etrolizumab (29.6%) was not significantly different from the placebo group (20.6%; P=0.19). Most adverse events were not serious and low-grade (grades 1/2). No deaths or cases of progressive multifocal leukoencephalopathy were observed.

Despite nominally significant benefits with etrolizumab versus placebo in endoscopic improvement, endoscopic remission, and histologic remission in this cohort of TNF-naïve patients, the primary endpoint of remission at week 62 among week 10-responders was not met. No new or unexpected safety signals occurred, and most adverse events were low-grade.

1. Vermeire S. Etrolizumab versus placebo in tumor necrosis factor antagonist naïve patients with ulcerative colitis: results from a randomized phase 3 LAUREL trial. UEG Week Virtual Symposium 2020, abstract LB18.

13. Cholecystectomy does not affect mortality in elderly patients

Cholecystectomy is often recommended after treatment for common bile duct stones. However, especially in the elderly, it is difficult to decide whether to recommend cholecystectomy. A study from Japan showed that the presence or absence of cholecystectomy does not affect biliary tract problems or mortality in patients ≥80 years old [1].

Patients with choledocholithiasis have been shown to have a high incidence of acute cholecystitis after endoscopic treatment of bile duct stones. This study assessed the necessity of cholecystectomy for gallstones after treatment of choledocholithiasis in elderly patients aged ≥80 years. The rate of biliary troubles and mortality according to the presence or absence of cholecystectomy were studied as well.

Of the 314 patients who underwent endoscopic retrograde cholangiopancreatography for common bile duct stones in a Japanese hospital over 5 years (2011-2016), 197 patients had gallstones. The current retrospective analysis compared 106 cases aged ≤79 years (young group) with 91 cases aged ≥80 years (elderly group). The patient background differed between both groups regarding sex ratio and mean common bile duct diameter. The mean observation period was not different in both groups.

Cholecystectomy was performed in 51% of the young group and 9% of the elderly group. The rate of surgery was significantly lower in the elderly group. Postoperative biliary troubles occurred in 18% of the young group and 30% of the elderly group. Cholecystectomy significantly reduced the risk of biliary problems in the young group, but there was no significant difference in mortality. There were no significant differences in biliary trouble and death in the elderly group.

This study showed that the presence or absence of cholecystectomy does not affect biliary tract problems or death in elderly people ≥80 years old. Follow-up may be appropriate without surgery. Further studies with larger sample sizes are needed.

1. Kodama R. Study of the necessity of cholecystectomy after treatment of choledocholithiasis for elderly patients. UEG Week Virtual Symposium 2020, abstract OP187.

14. Probiotic provides a potential adjuvant treatment to gluten-free diet

In the duodenum of patients with celiac disease, the expression of the human serine protease inhibitor elafin is decreased. The appearance of the probiotic *Bifidobacterium longum* NCC2705 in duodenal aspirates was associated with a simultaneous increase in the concentration of serpin, a bacterial homologue of elafin, in patients with celiac disease or non-celiac gluten sensitivity [1].

Celiac disease is a chronic autoimmune enteropathy triggered by gluten ingestion. Non-celiac gluten sensitivity is an emerging symptom-based condition, triggered by the ingestion of wheat and related cereals, but in the absence of celiac disease or wheat allergy. The standard treatment of these 2 conditions is a gluten-free diet. However, adherence to a strict gluten-free diet is challenging due to accidental gluten intake.

In a previous mouse model of celiac disease, *B. longum* NCC2705 was shown to ameliorate gluten immunopathology through the production of serpin. However, its effects on humans have never been tested. The current placebo-controlled, cross-over trial evaluated the safety and gastrointestinal tolerability of *B. longum* NCC2705 in patients with celiac disease who were following a gluten-free diet for ≥1 year (n=18) and participants with self-diagnosed non-celiac gluten sensitivity who were on a gluten-free diet for ≥6 weeks (n=20). After intake of the probiotics on the test day, *B. longum* NCC2705 was detected in duodenal aspirates in both groups. In parallel, the serpin concentration significantly increased by 36% compared with placebo (P=0.016).

No serious adverse events (AEs) were recorded. Other AEs and gastrointestinal tolerability parameter scores (nausea, flatulence, bowel sounds, abdominal cramping, diarrhoea, and vomiting) did not differ between probiotic and placebo groups.

The current study showed that the appearance of *B. longum* NCC2705 in duodenal aspirates was associated with a concomitant increase in serpin concentration. This provides a mechanistic basis for the potential use of this probiotic as an adjuvant treatment to a gluten-free diet to protect from accidental gluten intake. Furthermore, this probiotic was well tolerated and safe for human consumption.

1. Otten B. Safety of *Bifidobacterium longum* NCC 2705 and production of its serpin in patients with celiac disease and non-celiac gluten sensitivity. UEG Week Virtual Symposium 2020, abstract OP174.

15. Low-FODMAPs diet does not improve PPI-refractory GERD

An open-label study from France showed that a low-FODMAPs (Fermentable Oligo-, Di-, Mono-saccharides and Polyols) diet did not have any benefit over a standard diet to improve symptoms in patients with proton pump inhibitors (PPI)-refractory gastro-oesophageal reflux disease (GERD).

Dietary advice is often proposed for patients with GERD. Previous studies demonstrated that a low-FODMAPs diet improved lower gastrointestinal symptoms. Colonic fermentation of alimentary carbohydrates has been shown to impact gastric and oesophageal motility and the occurrence of reflux episodes.

The current multicentre, randomised, open-label study from France compared the efficacy of a 4-week low-FODMAPs diet with a standard diet in 31 patients (55% female, median age 45 years) with symptomatic PPI-refractory GERD, defined by a Reflux Disease Questionnaire (RDQ) score >3 and abnormal pH-impedance monitoring on PPIs [1].

Adherence to the assigned diet was good. There was a significant difference in the amount of FODMAPS consumed per day between the low-FODMAPs diet and the standard diet group (2.5 g vs 13 g, respectively; P<0.001). Furthermore, the caloric intake decreased in both groups (from 1,600 to 1,400 kcal on average, P<0.001) without significant differences between the 2 groups. There was also no significant difference in response rates (RDQ score ≤3) between the low-FODMAPs diet and standard-diet groups (37.5% vs 20%; P=0.20).

The primary endpoint was the percentage of responder patients (RDQ ≤3) at the end of the 4 weeks. Total RDQ score and dyspepsia subscore decreased significantly over time in both groups (P=0.002) These was no difference according to the assigned diet group (P=0.85).

The secondary endpoints evaluated the effect of the diet on pH-impedance parameters and associated functional symptoms (dyspepsia, irritable bowel syndrome [IBS]), using different scores, including the Gastrointestinal Quality of Life Index (GIQLI) and the IBS-Severity Scoring System (IBS-SSS).

The IBS-SSS decreased in both groups, but this was only significant for the FODMAPS group (P=0.04). There was no difference in the GIQLI score. Moreover, there was no significant difference in the pH-impedance parameters between the low-FODMAPs diet and standard diet.

This study demonstrated that a low-FODMAPs diet did not show any benefit over a standard diet to improve symptoms in patients with PPI-refractory GERD.

1. Zerbib F. Low-FODMAPS diet for the treatment of refractory gastroesophageal reflux disease. A randomized controlled trial. UEG Week Virtual Symposium 2020, abstract OP194.