Mirikizumab Resolves Inflammation in UC
Almost two-thirds of patients with ulcerative colitis respond to mirikizumab treatment at 12 weeks in the phase 3 LUCENT-1 study.

H. pylori Eradication in Aspirin Users Reduces Ulcers
Patients on long-term medication with aspirin suffer from less upper GI ulcer bleeding after eradication treatment for H. pylori. The benefit disappeared after 2.5 years.

Cirrhotic Patients Urgently Need Third SARS-CoV-2 Vaccine
Cirrhotic patients showed insufficient T cell reactivity after 2 mRNA vaccine doses, but a booster vaccine led to significantly higher antibody levels.
Contents

Letter from the Editor

3 IBD in 2022
S1P Receptor Modulators
3 Fast recapture of response with ozanimod after withdrawal in UC
3 Ozanimod caused substantial response after failure to induction
4 Etrasimod shows advantage over placebo in UC
4 Etrasimod reduces adaptive immune cells in the periphery in UC

Interleukin Inhibitors
5 Favoursable risankizumab maintenance rates in delayed responders
6 IL-23 inhibition reduces inflammatory biomarkers in pre-treated UC
6 Maintained symptom control with mirikizumab in UC
7 Mirikizumab successfully resolves active histologic inflammation in UC

Small Molecules
8 Upadacitinib for CD: remarkable efficacy in induction therapy
8 Sustained maintenance results with upadacitinib in UC
9 Start low with brepocitinib and ritlecitinib in UC
10 Another chance for TYK2 inhibition in UC
11 Small molecule ofezazimod shows promise in UC

Anti-integrins
11 Pivotal results of etrolizumab for CD partly disappointing
12 Better results for vedolizumab in early CD

Treatment Strategies
13 Some patients with limited CD may benefit from an early surgical intervention
13 Dose-interval of adalimumab may be prolonged in stable remission

14 What Is Hot in Upper GI Disorders?
14 Less ulcer bleeds early after H. pylori eradication in aspirin users
15 Dupilumab effective in paediatric patients with eosinophilic oesophagitis
16 Neoplasia in Barrett’s oesophagus benefits from early intervention

17 Hepatology in 2022
17 Portal hypertension is associated with poor prognosis in cirrhotic patients
17 Transplant-free survival enhanced by colectomy with ileostomy
18 SARS-CoV-2: Booster doses of key importance for cirrhotic patients

19 What Is New in Pancreatic Cancer and Pancreatitis?
19 Procalcitonin-based algorithm to guide antibiotic use
19 Fewer long-term interventions after delayed drainage in necrotising pancreatitis
20 Detection of Europe’s deadliest cancer: much room for improvement

21 Colorectal Carcinoma: Improving Diagnosis and Therapy
21 Immunotherapy response may be modulated by microbiome
22 Computer-aided colonoscopies improved adenoma detection rates
23 Benefit of colon cancer screening with colonoscopy lower than anticipated
23 Screening-detected colorectal cancers may have superior surgical outcomes
Dear colleagues,

30 years of UEG was celebrated during the UEG Week 2022 in Vienna this year. For this conference, more than 10,800 individuals from over 116 countries registered, of which 20% attended the first-ever hybrid UEG Week conference online.

Of the almost 3,000 submitted abstracts, 1,760 abstracts were presented and the scientific programme consisted of more than 200 live-streamed sessions. We have managed to make a selection of the finest presentations in this peer-reviewed conference report. Our primarily focus was new data and insights in the field of IBD but we also included presentations on colorectal carcinoma, hepatology, pancreatitis and pancreas cancer, as well as upper GI disorders including neoplasia in Barrett’s oesophagus and eosinophilic oesophagitis. In the case you would like to ‘ingest more science’, please note that almost 700 presentations were recorded, of which many can still be accessed via the UEG library.

I would like to end by citing Helena Cortez-Pinto, current UEG president, who commented during the 30 years of UEG anniversary session: ‘We should be incredibly proud of what we, as a community, have achieved’. We should be, keep up the good work and let’s meet again next year in Copenhagen!

Sincerely,

Marjolijn Duijvestein
**S1P Receptor Modulators**

**Fast recapture of response with ozanimod after withdrawal in UC**

Post-hoc analysis of the True North trial, in patients with active ulcerative colitis (UC) who relapsed after withdrawal of ozanimod during the maintenance period, investigated their response after re-introduction of the medication. Almost 60% of these patients recaptured clinical response within 10 weeks of re-initiation.

In the True North trial (NCT02435992), treatment with the selective, sphingosine-1-phosphate (S1P) receptor modulator ozanimod demonstrated significant improvements regarding the incidence of clinical remission and key secondary clinical, endoscopic, and histologic endpoints among patients with UC [1]. These endpoints were assessed after 10 weeks, at the end of the double-blind induction period, and after 52 weeks of treatment, at the end of the maintenance period [1]. Dr Anita Afzali (University of Cincinnati College of Medicine, OH, USA) presented a post-hoc analysis from the True North open-label extension (OLE) study, to assess recapture of response in patients who lost response while receiving placebo during the True North maintenance period and subsequently received ozanimod in the OLE [2].

In the True North study, participants were randomised 2:1 to receive double-blind ozanimod 0.92 mg or placebo (cohort 1) or open-label ozanimod 0.92 mg (cohort 2). Participants who achieved clinical response with ozanimod at the end of the induction period at 10 weeks (n=457) were re-randomised to placebo during the maintenance period of 42 weeks (n=227). Those who experienced disease relapse after discontinuing the treatment (n=77) subsequently received open-label re-induction with ozanimod.

Compared with all ozanimod-treated participant groups at induction baseline (cohort 1 and 2), a higher proportion of participants who lost response on placebo during the maintenance period were receiving corticosteroids at screening (41.6% vs 30.5% for cohort 1 and 36.2% for cohort 2) and had a history of prior biologic use (49.4% vs 32.4% for cohort 1 and 43.9% for cohort 2). More than half of the patients in this subgroup (56%; 43/77) achieved symptomatic clinical response within 5 weeks of re-initiating open-label ozanimod and maintained it until 10 weeks of the OLE (58%; 45/77). The response rates were similar in biologic-naïve participants and participants with prior biologic exposure. The mean partial Mayo score and subscores (rectal bleeding, stool frequency subscore, and Physician’s Global Assessment) decreased 5 weeks after the reintroduction, and further reductions occurred at week 10 of the OLE.

The authors concluded that almost 60% of participants who relapsed after ozanimod withdrawal during True North’s randomised maintenance period recaptured symptomatic clinical response by 10 weeks after ozanimod re-initiation. Furthermore, most of them presented these responses as early as 5 weeks after re-initiation.


**Ozanimod treatment prompted substantial response after failure of response to induction**

Continued ozanimod treatment for the induction of non-responders in the phase 3 True North trial, induced symptomatic clinical response in nearly half of the patients with ulcerative colitis (UC) after 10 weeks in an open-label extension trial (OLE). Furthermore, clinical remission was reached by 19.3% at this timepoint.

“Ozanimod is an oral, sphingosine-1-phosphate (S1P) receptor modulator that selectively targets S1P1 and S1P5 and is approved by the European Union and the USA for the treatment of moderately to severely active UC,” Prof. Remo Panaccione (University of Calgary, Canada) informed [1]. The compound has been evaluated in the randomised, phase 3 True North trial (NCT02435992), which found it to be significantly beneficial over placebo in clinical, endoscopic, and histologic measures. The 150 post-induction non-responders from cohort 1 of the True North trial were enrolled in the OLE. At baseline of True North, the OLE cohort had a mean age of 38.6 years, participants were diagnosed with UC at a mean of 6.6 years ago, and 66% were men. Extensive
disease was present in 44%, one-third of the participants used corticosteroids, and 36.7% had been exposed to a TNF inhibitor. The mean total Mayo score was 9.2 at baseline, which was slightly improved to 8.5 at week 10.

At weeks 5 and 10 of the OLE, symptomatic clinical response was attained by 44.0% and 48.7% of the previous non-responders, respectively. Stratifying according to prior biologic exposure resulted in similar proportions achieving symptomatic clinical response: 43.7% for bio-naïve and 45.2% for bio-exposed at week 5, along with 48.3% and 50.0% at week 10, respectively. Due to the relatively small subgroups, further predictive analyses on that effect are scheduled. Prof. Panaccione also remarked that the higher bar of symptomatic clinical remission was achieved by an additional 16.0% at week 5, which increased to 19.3% at week 10.

“In conclusion, patients with moderately to severely active UC, who failed to respond to an initial 10 weeks of ozanimod, may benefit from an additional 5 to 10 weeks of treatment,” Prof. Panaccione stated.

1. Panaccione R, et al. Extended therapy with ozanimod for delayed responders to ozanimod in moderately to severely active ulcerative colitis: data from the True North open-label extension study. OP196, UEG Week 2022, 8–11 October, Vienna, Austria.

Etrasimod shows advantage over placebo in UC

In 2 phase 3 studies that comprised 2 outcomes of clinical remission for induction at week 12 and 1 endpoint at week 52, etrasimod demonstrated a significant benefit for patients with ulcerative colitis (UC). Key secondary endpoints were also met.

The selective sphingosine-1-phosphate (S1P) receptor modulator etrasimod was assessed for its potential benefits in treating adult patients with UC in the phase 3 ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) trials [1]. ELEVATE UC 52 had a so-called ‘treat-through’ design: the included 433 patients were randomised 2:1 to 2 mg of etrasimod or placebo and the co-primary endpoint was clinical remission at week 12 and week 52; patients who did not improve within the induction period were allowed to switch and be enrolled in the open-label extension study ELEVATE UC OLE (NCT03950232) at week 12. In ELEVATE UC 12, 354 adult patients were treated with 2 mg of etrasimod orally or placebo and the study was completed after 12 weeks with the primary endpoint being clinical remission, defined via the modified Mayo score (stool frequency subscore 0/1, rectal bleeding 0, endoscopic subscore of 0/1).

All participants were 16–80 years old, had moderate-to-severe UC, and a history of inadequate or loss of response to at least 1 treatment for UC, but not more than 2 biologics or 1 biologic and 1 JAK inhibitor. The demographics were well balanced across the different arms. On average, the disease duration was 7 years, about one-third of patients had extensive colitis, and the median Mayo score was 7. Between 51.7% and 61.1% of participants had a baseline endoscopic score of 3. Looking at prior treatment, 60% of participants were naive and 40% were exposed; one-third was on concomitant steroids.

Clinical remission rates in ELEVATE UC 52 were statistically significant both at week 12 and week 52: 27% for etrasimod versus 7.4% for placebo and 32.1% for etrasimod versus 6.7% for placebo, respectively (P<0.001 for both comparisons). Also, key secondary endpoints like endoscopic improvement, symptomatic remission, and steroid-free remission were all positive. “There was not a single endpoint that was not met,” Prof. Séverine Vermeire (University Hospital Leuven, Belgium) summarised. In ELEVATE UC 12, both primary and secondary endpoints showed significant superiority of etrasimod over placebo.

“In both studies, treatment with etrasimod 2 mg daily resulted in clinically meaningful and statistically significant improvements in all pre-defined outcomes at week 12 and week 52,” Prof. Vermeire concluded.

1. Sandborn WJ, et al. Etrasimod 2mg once daily as treatment for moderately to severely active ulcerative colitis: results from the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials. OP086, UEG Week 2022, 8–11 October, Vienna, Austria.

Etrasimod reduces adaptive immune cells in the periphery in UC

An exploratory analysis of the ELEVATE UC trials revealed that therapy with etrasimod has a rapid and differential effect on the frequency of circulating immune-cell subsets in the peripheral blood of patients with moderately to severely active ulcerative colitis (UC). Consistent with its proposed mechanism of action, etrasimod reduced T and B cells in the periphery, with a greater impact on CD4+ cells than on CD8+ cells.

1. Sandborn WJ, et al. Etrasimod 2mg once daily as treatment for moderately to severely active ulcerative colitis: results from the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials. OP086, UEG Week 2022, 8–11 October, Vienna, Austria.
Etrasimod is an investigational, once-daily, oral, selective sphingosine-1-phosphate (S1P) receptor modulator. Etrasimod partially and reversibly sequesters specific lymphocyte subsets in the lymph nodes, reducing circulating lymphocytes and resulting in fewer immune cells available to traffic to the GI tract [1]. However, the mechanism of action is unknown in patients with UC. The agent has already demonstrated efficacy in adults with moderately-to-severely active UC in the phase 3 ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) trials [2,3]. In healthy volunteers, etrasimod has shown selective effects on adaptive immune cells, in particular CD4+ cells [4]. To further explore the effect of etrasimod on immune-cell subsets in UC, Prof. Silvio Danese (Vita-Salute San Raffaele University, Italy) performed a per-protocol, exploratory analysis of data from the ELEVATE UC 52 and ELEVATE UC 12 studies [5]. Whole blood was collected at weeks 2, 4, 8, and every 4 weeks up to week 52 in the ELEVATE UC 52 trial and at weeks 2, 4, 8, and 12 in the ELEVATE UC 12 trial for assessment of absolute lymphocyte counts and immunophenotyping.

Participants treated with etrasimod demonstrated nearly nadir (i.e. lowest point) absolute lymphocyte counts by week 2, which was maintained during the treatment period through week 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12. In addition, treatment with etrasimod resulted in rapid mean percentage reduction from baseline to week 2, with nadir and near nadir changes reached by week 4 in both trials for total T cells, T-helper cells, cytotoxic T cells, and B cells. All reductions were maintained throughout the studies. In contrast, etrasimod did not influence natural-killer cells or monocytes in either study.

These results indicate that etrasimod has a rapid and differential effect on the frequency of circulating immune-cell subsets in the peripheral blood of patients with moderately-to-severely active UC, through sequestration of lymphocytes in the lymph nodes. Etrasimod reduced adaptive immune cells (T and B cells) in the periphery, with a greater impact on CD4+ cells than on CD8+ cells but spared innate immune cells that are important components of immune surveillance.

5. Danese S, et al. Effect of etrasimod on circulating lymphocytes in patients with moderately to severely active ulcerative colitis: data from the phase 3 ELEVATE UC 52 and ELEVATE UC12 trials. MP246, UEG Week 2022, 8–11 October, Vienna, Austria.

**Interleukin Inhibitors**

**Favourable maintenance rates for risankizumab also in delayed responders with CD**

After 1 year of maintenance on 360 mg of subcutaneous risankizumab, 75.8% of patients with Crohn’s disease (CD) who had required a second induction period were in clinical response. In the cohort of these delayed responders, about 40% also reached the outcome of deep remission after continued risankizumab treatment up to a year.

In the phase 3 ADVANCE (NCT03105128) and MOTIVATE (NCT03104413) trials, patients with CD who did not respond to a first induction of 12 weeks with the IL-23 inhibitor risankizumab, received a second 12-week period of induction treatment. Those who achieved a ≥30% decrease of average daily abdominal pain score (APS) and/or a ≥30% reduction in their average daily stool frequency (SF) and/or a ≥30% reduction in their average daily abdominal pain score (APS) were called ‘delayed responders’ and were eligible to enter the FORTIFY trial (NCT03105102). These patients continued to receive either 180 or 360 mg of intravenous risankizumab. Prof. Geert D’Haens (Amsterdam UMC, the Netherlands) shared results on the long-term efficacy and safety of risankizumab at week 52 of maintenance treatment in those ‘delayed responders’ [1].

The analysis included 63 participants (30 on 180 mg, 33 on 360 mg) with an average age between 38.5–40.4 years, and 36.4–40.0% were women. Most participants had a history of failure to anti-TNF treatment (Anti-TNF History failure of 1: 72.2% [180 mg group] and 62.5% [360 mg group], Anti-TNF History failure of >1: 27.8% [180 mg group] and 37.5% [360 mg group], but also previous therapy with vedolizumab (failure 38.9% and 25% for low and high dose group) or ustekinumab (failure 16.7% and 12.5% for low and high dose group) or ustekinumab was reported. Mean Crohn’s Disease Activity Index (CDAI) was 288.7 and 291.1 for the low- and high-dose group and mean Simple Endoscopic Score for Crohn’s Disease (SES-CD) was 11.6 and 13.6, respectively.

At week 52, a CDAI response (CDAI ≥100 points from baseline of the induction study) was present in 53.3% (180 mg) and 75.8% (360 mg) of the participants, while 56.7% and 66.7% achieved CDAI remission (CDAI <150). Clinical remission rates in the SF/APS outcome (average daily SF ≤2.8 and not worse than baseline and average daily AP score ≤1 and not worse than baseline) were 43.3% on the lower
and 54.5% on the higher dose (see Figure). "Of course, the study was not powered to show a dose-response curve, but there is a numerical superiority for the higher dose of risankizumab. Remember that these are kind of refractory patients, they needed 2 induction treatments before they had a significant drop in their CDAI," Prof. D’Haens commented. In the composite endpoint of deep remission (CDAI clinical remission plus endoscopic remission), rates of 40.0 and 39.4% were observed for the 180 mg and 360 mg regimens. The respective results for endoscopic response and endoscopic remission in the 360 versus the 180 mg arms were 45.5 versus 36.7% and 42.4 versus 40.0%. An ulcer-free endoscopy was attained by 24.2% (360 mg) and 27.6% (180 mg). The safety summary did not reveal new safety risks and risankizumab was overall well tolerated.

Figure: Clinical endpoints at week 52 in risankizumab delayed responders [1]

<table>
<thead>
<tr>
<th></th>
<th>CDAI clinical remission (%)</th>
<th>Enhanced clinical response (%)</th>
<th>CDAI clinical remission (%)</th>
<th>SF/APS clinical remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 52</td>
<td>53.3</td>
<td>66.7</td>
<td>53.3</td>
<td>66.7</td>
</tr>
<tr>
<td>Week 52</td>
<td>54.5</td>
<td>67.1</td>
<td>54.5</td>
<td>67.1</td>
</tr>
<tr>
<td>Risankizumab 180 mg SC</td>
<td>36/30</td>
<td>52/52</td>
<td>36/30</td>
<td>52/52</td>
</tr>
<tr>
<td>Risankizumab 360 mg SC</td>
<td>31/31</td>
<td>43/43</td>
<td>31/31</td>
<td>43/43</td>
</tr>
</tbody>
</table>

“These findings underscore an additional clinical benefit of initiating maintenance dosing of subcutaneous risankizumab, following intravenous induction, even in the patients who do not respond after 12 weeks," Prof. D’Haens concluded.

1. D’Haens G, et al. 52-weeks risankizumab subcutaneous maintenance dosing is efficacious and well tolerated in patients with moderate-to-severe Crohn’s disease who had delayed response to 12 weeks IV risankizumab induction. OP126, UEG Week 2022, 8–11 October, Vienna, Austria.

**IL-23 inhibition reduces inflammatory biomarkers in pre-treated UC**

Therapy with guselkumab led to an early and consistent reduction of inflammatory biomarkers starting from week 4 through week 12 in patients with ulcerative colitis (UC). A higher percentage of patients treated with guselkumab achieved normalisation of biomarkers at week 12.

The QUASAR induction study 1 (NCT04033445) is a phase 2b study of the IL-23 inhibitor guselkumab (in 2 doses) as induction therapy in patients with moderately to severely active UC who had an inadequate response or intolerance to conventional therapy (e.g. thiopurines or corticosteroids) or advanced therapy (e.g. TNF blockers, vedolizumab, or tofacitnib). Results from the induction phase at week 12 demonstrated that treatment with guselkumab resulted in greater improvements across key clinical and endoscopic/histologic outcome measures compared with placebo [1]. C-reactive protein (CRP) and faecal calprotectin (FCP) are both non-invasive, inflammatory biomarkers indicating disease activity in patients with IBD. Therefore, the influence of guselkumab treatment on these biomarkers was also assessed in the QUASAR study [2].

A total of 313 participants were included in the analysis, 83% had severe disease and 52% had inadequate response to previous therapy. Half of the study population had already failed 1 advanced therapy, mostly TNF blockers, 33.3% had failed 2 advanced therapies.

Median concentrations of both biomarkers were similar across groups (guselkumab 200 mg, guselkumab 400 mg, and placebo) at baseline. Starting from week 4 throughout week 12, greater median reductions in both CRP and FCP concentrations were seen in participants treated with guselkumab compared with placebo: median changes from baseline to week 12 in CRP were -1.86 mg/L for the combined guselkumab group compared with 0.06 mg/L for placebo only (nominal P<0.001). Similarly, FCP concentrations dropped by -684.00 mg/kg at week 12 in the combined guselkumab group compared with 0.00 mg/kg in the placebo group (nominal P<0.001). Consequently, 44% of participants treated with guselkumab achieved normal CRP concentrations (≤3 mg/L) compared with 18.8% in the placebo group (nominal P<0.001). At baseline, median CRP concentrations in the total study population were 5.1 mg/L. The corresponding values for FCP (≥250 mg/kg) were 33.0% versus 9.9% (nominal P<0.001). A dose-dependent effect between the low and high guselkumab dose could not be detected.

1. Panés J, et al. The effect of guselkumab induction therapy in patients with moderately to severely active Ulcerative Colitis: QUASAR phase 2b induction results at week 12 by prior inadequate response or intolerance to advanced therapy: OP109, UEG Week 2022, 8–11 October, Vienna, Austria.

**Maintained symptom control with mirikizumab in UC**

Patients with moderate-to-severe ulcerative colitis (UC) demonstrated sustained symptom control after response to induction therapy with mirikizumab. Stool
frequency remission and rectal bleeding remission were maintained at week 40 in over three-quarters of patients. Mirikizumab, a monoclonal antibody against the p19 subunit of IL-23, has shown superior efficacy over placebo in patients with moderately to severely active UC in the LUCENT 1 induction trial (NCT03518086) [1–3]. Furthermore, there were positive results for the maintenance of clinical remission at week 40 in the phase 3 LUCENT 2 study (NCT03524092) [4]. Prof. Axel Dignass (Agaplesion Markus Hospital, Germany) presented a new analysis of LUCENT 2 that focussed on symptom control maintenance [1].

“This is a fairly severe patient population with UC,” Prof Dignass commented on the study cohort at baseline of LUCENT 1. Among the disease characteristics were a mean disease duration between 6.7 and 6.9 years, a mean modified Mayo score of around 6.5, a median bowel urgency severity of 6.0, and a mean abdominal pain of 4.9 and 5.3 on a numeric rating scale. “There is pancolitis seen in one-third of the patients and if you look at the endoscopic Mayo score, you see that about half of the patients had a severe activity,” Prof. Dignass further specified. More than one-third of the patients had prior failure to a biologic or tofacitinib treatment. LUCENT 2 randomised 544 responders of the LUCENT 1 trial 2:1 to maintenance treatment of 200 mg mirikizumab or placebo every 4 weeks.

After 40 weeks of maintenance, stool frequency remission was attained by 75.1% in the mirikizumab arm compared with 44.7% on placebo (P<0.001). Rectal bleeding remission was achieved by 79.7% in the intervention arm versus 49.7% on placebo (P<0.001). Symptomatic remission, consisting of stool frequency plus rectal bleeding remission, was observed for 71.0% of the study drug arm and 39.7% in the placebo arm (P<0.001). Furthermore, 69.7% versus 38.4% had stable symptomatic remission at week 40 of maintenance (P<0.001), also favouring the group that had a total of 52 weeks of continuous mirikizumab therapy. As for bowel urgency remission, participants on mirikizumab profited of an additional 13.6% points in the first 2 months of maintenance. At week 40, 42.9% of participants on mirikizumab maintained bowel urgency remission compared with 25.0% on placebo (P<0.001). An improvement of ≥30% from baseline in abdominal pain was found for 76.2% and 47.2% (P<0.001) in the mirikizumab and placebo arms at week 40.

“In conclusion, a greater proportion of mirikizumab-treated patients could maintain their clinical improvements looking at the patient-reported outcomes and sustained maintenance of remission in UC symptoms including rectal bleeding, stool frequency, bowel urgency, and abdominal pain,” Prof. Dignass summarised.

Mirkizumab successfully resolves active histologic inflammation in UC

Significantly greater rates of histologic improvement, histologic remission, histologic-endoscopic mucosal improvement, and histologic-endoscopic mucosal remission were observed in patients with ulcerative colitis (UC) treated with mirikizumab versus placebo at week 12. Moreover, efficacy was consistently demonstrated in patients regardless of prior biologic or tofacitinib exposure/failure during induction and maintenance treatment with mirikizumab.

Mirikizumab is a monoclonal antibody against IL-23, an IgG4 antibody binding to the p19 subunit of IL-23. Prof. Fernando Magro (CHU de São João, Portugal) investigated whether mirikizumab can resolve active histologic inflammation [1].

Histologic and combined histologic and endoscopic endpoints in patients with moderately to severely active UC who receive mirikizumab treatment through week 52 were assessed. Data derived from the phase 3 LUCENT 1 study (NCT03518086) was used to evaluate the safety and efficacy of mirikizumab compared with placebo over a 12-week induction period. Participants who demonstrated a clinical response to mirikizumab in this trial at week 12 (n=544) were randomised 2:1 into a double-blind maintenance period, the LUCENT 2 trial (NCT03524092). In this trial, participants received 200 mg mirikizumab intravenously (n=365) or placebo (n=179) every 4 weeks, up to week 40.

Both at week 12 and 52, greater proportions of participants treated with mirikizumab achieved histologic improvement (Geboes ≤3.1), histologic remission (Geboes ≤2B.0), histologic-endoscopic mucosal improvement (Mayo endoscopic subscore [ES]=0/1 excluding friability + Geboes ≤3.1), and histologic-endoscopic mucosal remission (ES=0/1 excluding friability + Geboes ≤2B.0) compared with placebo (P<0.001 for each comparison). At week 40, a significantly greater proportion of participants treated with the IL-23 inhibitor achieved resolution.
of active histologic inflammation with absence of neutrophils in mucosa (as assessed by a histologic remission treatment difference of 22.5% with P<0.001 and a histologic-endoscopic mucosal remission treatment difference of 19.9% with a P<0.001).

The authors concluded that incorporation of histology and histologic-endoscopic outcomes as a potential treatment target could enhance the current treatment strategies in UC.


Small Molecules

Upadacitinib for CD: remarkable efficacy in induction therapy

U-EXCEL is already the second induction trial that demonstrated efficacy of upadacitinib with a fast onset of action in patients with moderate-to-severe Crohn’s disease (CD) at week 12. Although patients were intensively pre-treated, half of them achieved clinical and 28.9% of them endoscopic remission as early as week 12.

There is still a great unmet need for advanced therapies that provide rapid, robust, and sustained disease control for patients with CD. Previously, the JAK1 inhibitor upadacitinib has been shown to be effective in inducing clinical and endoscopic improvement, with an acceptable safety profile in the U-EXCEED study (NCT03345836). U-EXCEL (NCT03345849) is a second induction study in patients with moderately to severely active CD. All participants were required to have failed or be intolerant to conventional or biologic therapy. By week 12, 88.0% of the placebo group (n=155) and 93.7% of the upadacitinib group (n=328) completed the study. Almost half (45%) of the study population had already failed prior biologic therapy, in most cases a prior TNF blocker. The primary endpoints of U-EXCEL at week 12 were clinical remission measured by the Crohn’s Disease Activity Index (CDAI <150) and by the patient-reported symptoms of stool frequency/abdominal pain (SF/AP) and endoscopic response [1].

A significantly higher percentage of participants treated with upadacitinib achieved the co-primary endpoints compared with placebo: 49.5% of participants treated with upadacitinib achieved CDAI <150 compared with 29.1% in the placebo group (P<0.0001). The SF/AP clinical remission (average daily stool frequency ≤2.8 and average daily abdominal pain ≤1 and neither worse than at baseline) was 50.7% versus 22.2% (P<0.0001), for the upadacitinib and placebo group respectively. In addition, endoscopic response was significantly higher in upadacitinib-treated participants with a clinically relevant difference of 33% (P<0.0001), “I believe that the achievement of endoscopic response in CD in almost half of the participants is a unique achievement of efficacy in an induction trial,” said Prof. Julian Panés (Hospital Clinic Barcelona, Spain). A significant proportion of participants treated with upadacitinib achieved clinical response as early as week 2 and clinical remission at week 4. Among patients taking corticosteroids at baseline, a significantly higher proportion of participants receiving upadacitinib 45 mg achieved steroid-free clinical remission per CDAI and per SF/AP compared with placebo at week 12 (P<0.0001 vs placebo for each comparison). “Finally, as much as 28.9% of participants treated with upadacitinib achieved endoscopic remission at this early time point,” Prof. Panés pointed out.

Treatment-emergent adverse events were noted in 58.6% of participants on placebo compared with 62.8% in the upadacitinib arm, but there was no difference in serious adverse events between the groups, and no deaths occurred. A higher proportion of participants in the placebo arm reported worsening of UC (3.7% for upadacitinib vs 10.7% for placebo), whereas anaemia (6.3% for upadacitinib vs 4.5% for placebo) and acne (6.9% of the participants treated with upadacitinib vs 0.6% for placebo) were more frequent in the upadacitinib arm, a class-related effect as Prof. Panés pointed out. In addition, herpes zoster (2.9% for upadacitinib and 0% for placebo) was more frequent in the upadacitinib arm but there was no case of GI perforation.


Sustained maintenance results with upadacitinib in UC

Final results of the U-ACHIEVE Maintenance trial demonstrated superiority of upadacitinib over placebo in disease control of ulcerative colitis (UC), along with a favourable safety analysis. The primary and key secondary endpoints that comprised clinical, histological, and patient-reported outcomes were met.
Moderate-to-severe UC induction and maintenance therapy with the selective, JAK1-inhibiting, small molecule upadacitinib has been approved by the US FDA and as of recently also in Europe. Top abstract prize awardee Prof. Séverine Vermeire (University Hospital Leuven, Belgium) presented the final results from the U-ACHIEVE Maintenance study (NCT02819635) [1]. Included were 681 patients between 16 and 75 years of age with moderately to severely active UC who had responded to a 45 mg upadacitinib induction therapy within the 2 identical trials U-ACCOMPLISH (NCT03653026) and U-ACHIEVE Induction (NCT02819635). For U-ACHIEVE Maintenance, these responders were re-randomised to 3 study arms: placebo, upadacitinib 15 mg, or upadacitinib 30 mg. Clinical remission in the adapted Mayo score, including rectal bleeding, stool frequency, and endoscopic results, was the primary endpoint. Among the secondary endpoints were maintenance of response, steroid-free remission, and patient-reported outcomes.

The mean age at baseline ranged from 41.7 to 43.0 years, 35.1% to 44.8% were women, and disease duration was around 8 years. Prior treatment with at least 1 biologic agent was observed in 45.9% to 48.0% of participants.

As previously published, the primary analysis of the study that comprised the first 451 participants showed significant superiority of both 15 and 30 mg upadacitinib dosages over placebo [2]. These results were reinforced by the final analysis of all participants: 40.4% on 15 mg and 53.6% on 30 mg of upadacitinib reached clinical remission versus 10.8% on placebo (P<0.001 for both comparisons) [2]. Positive secondary endpoints for the 15 mg and the 30 mg regimens of upadacitinib included maintenance of clinical response (65.6% and 77.5% vs 21.5%; both P<0.001) and corticosteroid-free clinical remission (52.3% and 64.6% vs 18.8%; both P<0.001). Furthermore, upadacitinib achieved significant better results for endoscopic improvement and maintenance, endoscopic remission, and mucosal improvement and healing (P<0.001 for both dosages and all comparisons with placebo). Prof. Vermeire especially highlighted the significant reductions in bowel urgency in 53.8% (15 mg) and 66.9% (30 mg) of the participants on the study drug compared with 18.4% on placebo (both P<0.001).

“Both of the doses were well tolerated – we did not observe any new safety signals compared with the smaller primary analysis or other non-UC indications,” Prof. Vermeire summarised the safety assessment. This final analysis supports the favourable benefit-risk profile of upadacitinib as a maintenance treatment in patients with moderately to severely active UC.

1. Vermeire S. Efficacy and safety of upadacitinib maintenance therapy in patients with moderately to severely active ulcerative colitis: final results from the phase 3 U-ACHIEVE Maintenance study. OP001, UEG Week 2022, 8–11 October, Vienna, Austria.

**Start low with brepocitinib and ritlecitinib in UC**

Therapy with the oral, investigative agents brepocitinib and ritlecitinib improved clinical remission and modified clinical remission and endoscopic results in patients with moderate-to-severe ulcerative colitis (UC) over 32 weeks in the VIBRATO study. Interestingly, changes were more pronounced in patients that were treated with low doses in the induction phase of the trial.

Both the JAK3/TEC and the JAK1/TYK2 pathways are implicated in the pathogenesis of UC through regulation of pro-inflammatory cytokine signalling and CD8+ T-cell cytotoxicity. This was the rationale to assess the efficacy and safety of the JAK3/TEC inhibitor ritlecitinib and the JAK1/TYK2 inhibitor brepocitinib in patients with UC in the phase 2b VIBRATO study (NCT02958865). In this trial, both small molecules were more effective during the 8-week induction period compared with placebo, with an acceptable safety profile. Dr Kenneth Hung (Pfizer, MA, USA) pointed out that, in the induction phase, modified remission at week 8 was high, as 38% and 25.5% of patients achieved endoscopic improvement with ritlecitinib and brepocitinib respectively [1]. “Next we wanted to evaluate efficacy and safety in a 24-week period,” he explained.

In the 8-week induction phase, both agents were given in 3 doses (20, 70, or 200 mg ritlecitinib once daily or 10, 30, or 60 mg brepocitinib once daily) and compared with placebo once daily. In the chronic dosing therapy phase, all participants continued in their respective treatment cohorts to receive oral ritlecitinib 50 mg or brepocitinib 30 mg once daily for 24 weeks. At week 32, efficacy was assessed with the total Mayo score (primary endpoint), clinical remission, modified remission, and endoscopic improvement. A total of 279 participants received treatment in the chronic period. Baseline characteristics were generally similar across treatment groups. About 40% to 65% of patients had already received biologics.

“We saw great improvement from week 8 to 32 for those with lower induction dosing. However, for those cohorts with
higher induction doses, we saw that the improvement was less dramatic from week 8 to week 32,” Dr Hung explained the changes in the total Mayo score (see Figure).

Figure: Improvements in total Mayo Score after 32 weeks are more pronounced in patients treated with low induction doses [1]

Similar patterns were seen for clinical remission (defined as total Mayo Score ≤2; no individual subscore >1; rectal bleeding subscore=0) and modified remission (modified Mayo Score [total Mayo Score without Physician Global Assessment]; stool frequency subscore ≤1; rectal bleeding subscore=0; endoscopic subscore ≤1). Rates of clinical remission and modified clinical remission generally continued to improve in groups receiving a lower induction dose. “These improvements were somewhat blunted in the higher induction dose groups,” Dr Hung explained.

Therapy with both agents also led to endoscopic improvements (Mayo endoscopic subscore ≤1). Changes generally continued to improve from week 8 to 32 in groups receiving a lower induction dose. Again, this improvement was generally more modest from week 8 through 32 in higher induction dose groups.

Dr Hung pointed out that both drugs were relatively safe and well tolerated across the groups. The most commonly reported adverse events included chronic urticaria, nasopharyngitis, arthralgia, and pyrexia. Moreover, there were no clinically significant observations for laboratory parameters. No thromboembolic events or malignancies were reported during the chronic period. However, there was a herpes signal: 2 participants in the chronic period suffered from herpes simplex (1 in each arm), another 4 participants had herpes zoster in the chronic dosing period (3 in the ritlecitinib and 1 in the brepocitinib arm). Only 1 of these events was moderate, all others were mild and did not lead to treatment discontinuation.

These positive study results support the further development of ritlecitinib and brepocitinib in patients with moderate-to-severe UC.


Another chance for TYK2 inhibition in UC

In a post-hoc analysis of the LATTICE-UC trial, deucravacitinib showed to be active in participants with ulcerative colitis (UC) that had prior exposure to at least 1 biologic. Moreover, therapy significantly reduced interferon-responsive gene transcripts; these changes were associated with clinical response, suggesting a role for TYK2 inhibition in the therapeutic armamentarium of UC.

TYK2 mediates signalling of IL-12, IL-23, and type-1 interferon (IFN), which are all key cytokines in the pathogenesis of UC. Deucravacitinib is an oral, selective, allosteric inhibitor of TYK2 that is already approved by the US FDA for the treatment of adults with moderate-to-severe plaque psoriasis.

In the double-blind, placebo-controlled, centrally-read, phase 2 LATTICE-UC trial (NCT03934216), the efficacy and safety of deucravacitinib was assessed in patients with moderately to severely active UC and inadequate response, loss of response, or intolerance to at least 1 conventional or biologic therapy [1]. In this trial, the primary endpoint of clinical remission at week 12 was not met. However, a treatment effect was observed in participants with prior exposure to at least 1 biologic. Now, in a post-hoc analysis, Prof. Stephan Schreiber (University Hospital Schleswig-Holstein, Germany) evaluated the effect of deucravacitinib in biologic-exposed participants with moderately to severely active UC [2].

In the induction phase of LATTICE-UC, from week 0 to week 12, participants were treated with deucravacitinib 6 mg twice daily or placebo. After week 12, a maintenance treatment was performed for up to 52 weeks. Of 131 randomised participants, 48 (36.6%) were biologic-exposed and participants in the deucravacitinib group were heavier and had more often a modified Mayo score >7.

At week 12, clinical remission (primary endpoint) was achieved by 16.1% in the deucravacitinib group compared with 0% in the placebo group. Superior efficacy of the TYK2 inhibitor was also seen in clinical response (29.0% with deucravacitinib vs 12.5% with placebo) and endoscopic

---

**Figure:** Improvements in total Mayo Score after 32 weeks are more pronounced in patients treated with low induction doses [1]
improvement rates (25.8% vs 12.5%) in biologic-exposed participants. "Biomarkers also confirmed this clinical observation," Prof. Schreiber said, since a greater reduction in faecal calprotectin was observed with deucravacitinib versus placebo (P<0.05 at week 12).

"The most interesting part is the transcriptome analysis," Prof. Schreiber stated. Transcripts of IFN-responsive genes, such as IFI44L and CXCL10, were significantly reduced in colonic tissues at week 12 compared with baseline for deucravacitinib treatment, but not with placebo. The decreases in IFN-responsive genes were associated with clinical response or remission, suggesting that inhibition of TYK2 pathways may be beneficial in UC. "You see very clearly that patients that are successful, also show that imprint in their transcriptome-signatures," Prof. Schreiber said. He therefore concluded that these results provide evidence of inhibition of the TYK2 pathway and suggests that a higher dose of deucravacitinib needs to be examined for clinical efficacy in UC, a step that is now done in a follow-up trial.

2. Schreiber St, et al. Efficacy of deucravacitinib an oral, selective, tyrosine kinase 2 inhibitor, in patients with moderately to severely active Ulcerative Colitis and prior exposure to biologic therapy: subanalysis from the phase 2 LATTICE-UC study. OP198, UEG Week 2022, 8–11 October, Vienna, Austria.

Small molecule obefazimod shows promise in UC

In the open-label extension of a phase 2b induction trial of obefazimod in ulcerative colitis (UC), more than half of the patients gained clinical remission and about one-third endoscopic remission at week 48. Among the patients in clinical remission at this point, 48.2% had not yet achieved remission when entering the maintenance trial.

Obefazimod is a small molecule, entailing an upregulation of microRNA 124 and a consequent decrease in inflammatory cytokines and chemokines [1,2]. After positive results of a 16-week induction trial (NCT04023396) that assessed various treatment regimens in adult patients with moderate-to-severe UC, all participants were eligible to enter a 96-week, open-label extension [1]. In terms of a first evaluation of long-term efficacy and safety of once-daily 50 mg obefazimod, the 48-week interim data was presented.

Of the participants in the initial study cohort, 97.7% (n=217) took part in the open-label extension trial. The participants had a mean age of 42.1 years, were predominantly men, and had a median faecal calprotectin level of 204.7 µg/g. Nearly half used corticosteroids and 45.2% had been treated with biologics or JAK inhibitors before. For those who did not complete week 48, non-responder imputation was used.

At week 48, the rates of clinical remission and clinical response were 54.8% and 82.0%. The proportion of patients within these groups who experienced these outcomes de novo, meaning they had no remission or response after induction, were 48.2% and 76.3%. Endoscopic improvement was present in 61.3% of patients and endoscopic remission was achieved by 33.2%. Of these 2 outcomes, there were de novo rates of 54.6% and 30.3%, respectively. Overall, 124/217 participants in the extension cohort had a response after 8 weeks of induction. Of these primary responders, 66.1% were in clinical remission, 37.9% in endoscopic remission, and 70.2% demonstrated endoscopic improvement at week 48.

The safety analysis found 65% of participants with ≥1 treatment-emergent adverse event (TEAE), with serious TEAEs in 7.8%. The study had to be discontinued due to TEAEs in 6.9% of participants. Most frequent were COVID-19 and headache (both in 11.5%), as well as UC and nasopharyngitis (in 6.9% and 6.5%).

In conclusion, Prof. Séverine Vermeire (University Hospital Leuven, Belgium) and co-authors confirmed a long-term efficacy and a favourable safety profile of obefazimod at a dosage of 50 mg/day in this phase 2b trial. A global phase 3 induction and maintenance study will be initiated soon.


Anti-Integrins

Pivotal results of etrolizumab for CD partly disappointing

Only the maintenance results of the pivotal cohort of the BERGAMOT trial met their co-primary endpoint, whereas the outcomes of induction failed statistical significance at week 14 in patients with Crohn’s Disease (CD). Although the effect size was as anticipated, very high placebo rates impacted the difference between groups.

Etrolizumab is an anti-integrin with dual action that targets both α4β7 and αEβ7 selectively. "So, you have a mode of
In this cohort, 385 participants were initially randomised 3:3:2 to a 14-week induction with subcutaneous etrolizumab 105 or 210 mg, or placebo. Thereafter, etrolizumab responders, i.e. patients with a drop in Crohn's Disease Activity Index (CDAI) of ≥70 points, were re-randomised 1:1 to the lower dose of etrolizumab or placebo. The co-primary endpoints in the induction phase at week 14 were clinical remission and endoscopic improvement (etrolizumab 210 mg versus placebo). The maintenance study had the same co-primary endpoints at week 66, comparing those on etrolizumab 105 mg with the group that received an induction with the study drug and then continued on placebo until week 66.

The groups were balanced on their baseline characteristics. Between 36.6% and 42.4% of participants used corticosteroids, 24.7% to 32.7% used immuno-suppressants, and between 40.6% and 49.7% were anti-TNF-naïve. The co-primary endpoint of the induction trial was not met at week 14. "If we look at the effect size for etrolizumab, it's within the expected range: 33% for clinical remission, 27% for endoscopic improvement, but what is immediately clear is that the placebo response rates for remission and endoscopic improvement were very high," Prof. Vermeire commented, referring to the 29.2% and 21.6% of participants in the placebo arms also reaching these endpoints.

In contrast, the maintenance study was positive in both components of the co-primary endpoint. Clinical remission was reached by 35.0% on etrolizumab 105 mg and 24.0% on placebo (P=0.0088). Endoscopic improvement was attained by 23.6% in the study drug arm and 12.2% in the placebo arm (P=0.0026). "So, induction: primary endpoint not met, maintenance: primary endpoint met," Prof. Vermeire underlined. The key secondary induction endpoints were also not statistically significant. These outcomes were partly negative for maintenance with only some significant nominal P-values for endoscopic remission and steroid-free clinical remission.

In terms of adverse events, etrolizumab was overall well tolerated. "No real safety signal was observed, also no safety signal with respect to infections or serious infections," Prof. Vermeire highlighted.


Better results for vedolizumab in early CD
Prospective data of an interim analysis on vedolizumab comparing achievement of remission in early versus late Crohn's disease (CD) were clearly in favour of the early group. A combined clinical and endoscopic remission was reached by 47% of those with under 2 years of CD in contrast with 16% of those in the late CD study arm.

In the treatment of CD, vedolizumab has demonstrated efficacy both as induction and maintenance therapy [1,2]. "We know also that for other treatments, mainly anti-TNF where we have the most data, higher efficacy is observed in patients with a shorter disease duration, but we do not have prospective data on whether the same would be observed with vedolizumab in early CD," Prof. Geert D'Haens (Amsterdam UMC, the Netherlands) explained the reason for the investigator-initiated LOVE-CD trial [NCT02646683] [1].

The multicentre, international, open-label study compared the remission rates in patients with early and late moderate-to-severe CD who were treated with intravenous vedolizumab at a dose of 300 mg every 8 weeks up to week 52, after induction until week 14. Included early CD patients had their diagnosis <2 years ago and their treatment history only showed corticosteroids and/or immunomodulators. Late CD was defined as over 2 years of disease duration and prior therapy with immunomodulators and anti-TNF plus corticosteroids.

Prof. D'Haens underlined that a hard primary endpoint was chosen for LOVE-CD that combined steroid-free clinical remission and endoscopic remission, expressed in a Crohn's Disease Activity Index (CDAI) <150 and a Simple Endoscopic Score for Crohn’s Disease (SES-CD) ≤3.

The intention-to-treat population of the presented interim analysis, after the second endoscopy at 6 months, consisted of 47 participants with early CD and 110 with late CD. Baseline demographics in these 2 groups were a median age of 29 and 35.5 years, a median CDAI of 252 and 257, and a
SES-CD of 9 and 11, respectively. In the late group, disease duration varied between 3–41 years and anti-TNF-exposure was 80% for adalimumab and 77.3% for infliximab.

The combined primary endpoint was reached by a significantly higher proportion of the early CD group (47%), compared with 16% of the late CD group (P=0.0001). Also, secondary endpoints led to significantly superior results for the early CD arm: SES-CD=0 in 45% versus 15% (P=0.0001) and SES-CD ≤3 in 66% versus 34% (P=0.0002). As the trial is still ongoing, the results at week 52 will be available at a later stage.

Overall, 21 serious adverse events were observed within LOVE-CD, among them were exacerbation of disease, perianal abscess, and tibial plateau fracture, with 2 cases each. Prof. D’Haens confirmed that there were no strong signals towards new adverse events that were unknown with this mechanism of action.

“We can conclude that in moderate-to-severe CD, vedolizumab treatment in early CD was significantly better than in late CD, to obtain steroid-free clinical remission and endoscopic remission,” Prof. D’Haens ended his talk.

1. D’Haens GR, et al. Higher endoscopic and clinical remission rates with vedolizumab in early than in late Crohn’s disease: results from the LOVE-CD study (low countries vedolizumab n CD study). OP130, UEG Week 2022, Vienna, Austria, 8-11 October.

**Treatment Strategies**

**Some patients with limited CD may benefit from an early surgical intervention**

In a Danish cohort study, patients with limited Crohn’s disease (CD) who underwent early surgery had a lower cumulative risk of re-operation, consistent with a more benign postoperative disease course. Prospective studies are needed to define patient groups that will benefit most from a surgical intervention.

In patients with CD with limited (affected segment ≤40 cm) and predominantly inflammatory terminal ileitis for whom conventional treatment is not successful, laparoscopic ileocaecal resection has shown to be a valid therapeutic alternative in the LIRIC trial [1]. In this trial, surgery led to a durable treatment effect comparable with infliximab treatment for these patients. However, there is limited data on early surgery among CD patients in general. To investigate the disease course in CD patients who underwent early versus late major abdominal surgery, a nationwide cohort study was performed using data from the Danish National Patient Registry and the Danish National Prescription Registry [2]. Dr Melek Zahra Sarikaya (Sjælland Universitetshospital, Denmark) and her team identified all CD patients diagnosed between 1 January 1997 and 31 December 2015 in Denmark. Included patients were stratified according to the time of surgery: Group 1 included 493 patients with an initial surgery within 29 days after diagnosis, group 2 had initial surgery between 30 and 180 days after diagnosis, and the ‘late surgery’ group 3 consisted of 1,518 patients that underwent surgery more than 180 days after their diagnosis. The 3 groups were compared regarding the need for re-operation, hospitalisation, and medications.

In group 1, participants had a lower cumulative re-operation risk but a higher hospitalisation risk. In addition, there was a significant decrease in time to re-operation for procedures performed after 2005. The re-operation risk was similar in group 2, but markedly elevated in group 3. The risk of hospitalisation was similar in groups 2 and 3, but lower than in group 1. The cumulative risk of immunomodulator use was highest in group 3 until 5 years. However, cumulative risk of biological use was not statistically significant between the groups. After 2005, the cumulative risk of hospitalisation decreased around 20% (P<0.05) and increased for immunomodulator and biological use by around 10% (P<0.05).

Early-resected CD patients showed advantages like a lower cumulative risk of re-operation, consistent with a more benign postoperative disease course. Moreover, their cumulative risk of immunomodulator use is lower in the initial years after surgery. According to the authors, closer monitoring and a faster decision regarding surgery among CD patients in general may lead to better long-term outcomes.

2. Sarikaya MZ, et al. Disease course and treatment outcomes of Crohn’s disease patients with early or late surgery: a Danish nationwide cohort study from 1997 to 2015. MP195, UEG Week 2022, 8–11 October, Vienna, Austria.

**Dose-interval of adalimumab might be prolonged in CD patients in stable remission**

According to the results of an open-label trial, prolonging the dose interval from 2 to 3 and then to 4 weeks is possible in patients with Crohn’s disease (CD) in stable remission. This approach results in a similar rate of persistent flares and lower infection-related adverse events, but an increase in rescue medication use.
According to a retrospective study, dose de-escalation of adalimumab is possible in patients with CD [1]. One possible way of achieving this is simply increasing the dose interval. Possible advantages of this approach are decreasing adverse events linked to biological therapy. Cost-savings are another important advantage of a longer dose interval: “There are not only side effects for the patient, but also for society, because we know that with an increasing uptake of biologics, healthcare costs are rising rapidly,” Dr Reinier van Linschoten (Franciscus Gasthuis en Vlietland, the Netherlands) explained. An open-label, multicentre, randomised-controlled, non-inferiority LADI trial (NCT03172377) assessed the clinical outcomes of an increased adalimumab dose interval compared with conventional dosing in CD patients in stable remission [2]. All 174 participants were in steroid-free clinical remission while on adalimumab maintenance therapy (40 mg adalimumab, every other week, for at least 9 months). Participants were randomised to increase adalimumab dose interval from 2 to 3 and then to 4 weeks (n=113), or to continue the conventional dose interval of 2 weeks (n=61). The primary study endpoint was the incidence of persistent flares.

“A dose extension was possible in most of the patients in the intervention group, only 10% had to go back to the conventional dose interval,” Dr van Linschoten explained. Four patients in the intervention group and 1 patient in the control group were excluded from the analysis for not meeting the inclusion criteria. The cumulative incidence of persistent flares at week 48 in the intervention group (3/109) was non-inferior compared with the control group (0/60). In addition, the cumulative incidence of transient flares was similar between the groups (pooled adjusted risk difference [pARd] 2.68%; 95% CI -0.93–6.30; see Figure). At week 48, 92% of the control group and 72% of the intervention group were in clinical remission (pARd -16.3%; 95% CI -30.9 to -1.82). Neither disease activity nor quality-of-life significantly differed between the control and the intervention group. However, the intervention group used significantly more rescue medication. Participants in the intervention group showed an increase in GI disorders, mainly mild GI side effects. A difference was also noted regarding the infection-associated adverse events: Per 100 person-years, 60 infection-related adverse events occurred in the intervention group versus 75 in the control group.

Increasing the adalimumab dose interval is a possible treatment strategy. However, there are some negative consequences like an increase in escape medication and fewer patients in clinical remission at week 48,” Dr van Linschoten concluded. Therefore, this approach should be discussed individually with the patient.


What Is Hot in Upper GI Disorders?

Less ulcer bleeds early after H. pylori eradication in aspirin users

Patient on long-term medication with aspirin suffer from less upper GI ulcer bleedings after eradication treatment for Helicobacter (H.) pylori. However, the benefit disappeared after 2.5 years.

"Helicobacter pylori is a strong risk factor for ulcers and upper GI bleedings in patients taking low-dose aspirin, but there is limited data on the effect of H. pylori eradication and its contradictory effects,” Prof. Christopher Hawkey (Nottingham Digestive Diseases Centre, UK) introduced as background for the HEAT trial (NCT01506986) [1,2]. The study aimed to explore the effect of H. pylori eradication on hospitalisation for ulcer bleeding in aspirin users. “We also wanted to develop a method that could be used for other big studies, based on primary care, using routine clinical data,” Prof. Hawkey explained.

Patient screening was performed between 2012 and 2017 via electronic interrogation of primary clinical practice data...
Dupilumab effective in paediatric patients with eosinophilic oesophagitis

In the first phase 3 trial in paediatric patients with eosinophilic oesophagitis, therapy with the IL-4/IL-13 receptor blocker dupilumab led to a significant reduction of peak oesophageal intraepithelial eosinophil count compared with placebo at week 16. In addition, dupilumab showed a favourable safety profile with more patients in the placebo group discontinuing therapy due to adverse events.

Dupilumab, a fully-human, monoclonal antibody, blocks the shared receptor component for IL-4/IL-13, key and central drivers of type 2 inflammation, and might therefore be active in eosinophilic oesophagitis, a chronic, progressive, type 2 inflammatory disease. Indeed, in the phase 3 LIBERTY-EoE-TREET trial (NCT03633617), dupilumab already demonstrated clinically meaningful improvements in histological, symptomatic, and endoscopic outcomes in adolescents and adults with eosinophilic oesophagitis. As a result, the FDA recently approved dupilumab as the first and only agent for treatment of adults and children ≥12 years with eosinophilic oesophagitis.

The phase 3 EoE KIDS trial (NCT04394351) aimed to evaluate the efficacy, safety, and tolerability of dupilumab versus placebo in paediatric patients, aged 1–11 years, with active eosinophilic oesophagitis [1]. All included participants had to respond to proton-pump inhibitors. The study consists of 3 parts. In the double-blind part A, 102 participants were randomised 1:1:1 to 2 doses of dupilumab or placebo and treated for 16 weeks. In part B, all participants will be offered dupilumab, and part C will be an open-label extension period up to 108 weeks. Prof. Evan S. Dellon (University of North Carolina School of Medicine in Chapel Hill, NC, USA) focussed on the primary outcomes of part A at week 16, especially from the high-dose group, noting that parts B and C are still ongoing. All participants had to have baseline oesophageal biopsies with a peak intraepithelial eosinophil count ≥15 eosinophils (eos)/high power field (hpf) in ≥2 of the 3 oesophageal regions, but there was no symptom threshold to be included.

At week 16, 68% of participants treated with the higher dupilumab dose and 58% with the lower dose achieved the primary endpoint, a peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf compared with 3% on placebo (P<0.0001 for each comparison; see Figure). Dupilumab was also superior to placebo in a couple of secondary endpoints, such as the reduction of peak oesophageal intraepithelial eosinophil count at week 16 from baseline. This parameter was reduced by 86% in the higher dupilumab dose group and increased with 21% in the placebo group (P<0.0001). The high-dose dupilumab regimen reduced histologic scores at week 16. Regarding clinical symptoms, a numeric improvement was seen in the dupilumab group. Participants

in the dupilumab group gained 3.09 kg weight compared with 0.29 kg in the placebo group. Although this difference failed to reach statistical significance, Prof. Dellon described it as a “substantial increase in body weight, almost a normalisation”.

Figure: Dupilumab improved the proportion of participants achieving peak oesophageal eosinophil count ≤6 eos/hpf at week 16 [1]

![Graph showing response rates](image)

Eos, eosinophils; hpf, high power field; SC, sub-cutaneous.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Higher-exposure regimen</th>
<th>Lower-exposure regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>37</td>
<td>31</td>
</tr>
</tbody>
</table>

1. Biopsies were collected from 3 oesophageal regions (proximal, mid, distal) at screening and week 16 for histology.

The rate of adverse events and treatment discontinuation due to adverse events prior to week 16 were higher in the placebo groups compared with the dupilumab group.


Neoplasia in Barrett’s oesophagus: the earlier the intervention, the better the long-term outcome

Treatment types for the eradication of early Barrett’s oesophagus-associated neoplasia vary according to the severity of the lesions. When comparing long-term results of those with pre-neoplastic or very early forms of neoplasia with more advanced lesions, the more extensive intervention of endoscopic submucosal dissection (ESD) may not balance the risk of greater oncologic severity.

“Early Barrett’s oesophagus-associated neoplasia can be curatively treated by endoscopic resection with high success rates, especially if followed by ablation therapy; however, the choice of the resection method is still a matter of debate,” Dr Fadi Younis (University Hospital Hamburg-Eppendorf, Germany) explained [1]. The presented retrospective study investigated the long-term outcomes in patients with Barrett’s oesophagus-associated neoplasia when the choice of treatment with endoscopic mucosal resection (EMR) or ESD was lesion-based. The current guideline of the European Society of Gastrointestinal Endoscopy recommends EMR for visible lesions ≤2 cm with low probability of submucosal invasion and for larger or multifocal benign dysplastic lesions [2]. ESD is suggested in case of suspected submucosal invasion, lesion size >2 cm, and lesions in scarred or fibrotic areas.

The main study outcomes were defined as complete remission or eradication of the neoplasia (CE-N) and intestinal metaplasia (CE-IM) after ESD or EMR. The baseline characteristics showed a total of 364 participants of whom 268 had EMR and 96 ESD. Participants undergoing ESD had a greater extent of disease, more visible lesions, and more difficult interventions. "In the pre-resection and post-resection, we can see that they had 90% of adenocarcinoma in the final histology and they had more difficult interventions," Dr Younis further specified the post-interventional histology outcomes of the ESD participants. The rate of adenocarcinomas in histology after EMD was 65.3%. Looking at lesion morphology, however, no difference was detected between the groups.

The primary resection treatment of all cancers and high-grade dysplasias showed success rates of over 96% for initial CE-N in both groups and initial biopsy proven CE-IM in 85.5% (EMR) and 82% (ESD) of cases in the per-protocol analysis. In the intention-to-treat cohort, these percentages were lower with initial CE-N in 78.5% (EMR) and 72.2% (ESD) and CE-IM in 66.7% and 58.6%, respectively. The long-term follow-up revealed CE-N status 2 years after EMD in 92% (per-protocol) and 62% (intention-to-treat) compared with 89% (per-protocol) and 48% (intention-to-treat) in those who received ESD. After 5 years, complete eradication in the per-protocol and intention-to-treat analyses was still present in the EMD group with 85% and 43% versus 75% and 20% after ESD. Looking at the differences by Kaplan-Meier estimates for risk of recurrence, the curves showed a significant difference between the groups: at the point of longest follow-up, 11% of the EMR and 23% of the ESD participants had recurrent neoplasia (P=0.02).

As for adverse events, Dr Younis stated that the overall safety in the 2 groups was similar but participants with ESD had more refractory strictures which required stent insertions and operations.

"Allocation of EMR versus ESD works, but the biology also counts," Dr Younis expressed in his conclusion.


Portal hypertension is associated with poor prognosis in cirrhotic patients
A large analysis of healthcare records revealed that, despite optimal current care, the prospects are gloomy for adults and children with portal hypertension – independent of aetiology. This underlines the need for novel therapeutic options to improve long-term survival of these patients.

In 2017, the Global Burden of Disease study reported over 1.32 million cirrhosis-related deaths globally, which is approximately 2.4% of all deaths worldwide [1]. At present, there is limited data estimating the prognosis of portal hypertension in children. A retrospective cohort study was designed to assess the prevalence of prespecified aetiologies of cirrhosis-related portal hypertension and to compare the prognosis among children and adults [2]. Data was derived from the electronic healthcare record TriNetX’s Analytics. Data from January 2007 to December 2020 was included with ICD-10 codes of prespecified aetiological diagnoses associated with cirrhotic portal hypertension. Assessed were event rates for complications and recorded mortality occurring within a 24-month follow-up period.

The 3 most commonly occurring prespecified aetiologies in the adult cohort (n=60,579) were alcoholic liver disease, followed by chronic viral hepatitis and non-alcoholic steatohepatitis. In contrast, most cases in the paediatric cohort (n=1,679) occurred due to biliary atresia (23%), followed by primary sclerosing cholangitis (14%). In the paediatric cohort, almost half of the study population (49.1%) had a claim of at least 1 adverse event in 2 years of follow-up, most frequently variceal haemorrhage in 33.8% and liver transplant in 26.3%. A further 15.9% underwent variceal band ligation to prevent upper GI bleeding. The 24-month survival probability was below 70% in patients developing variceal haemorrhage without intervention.

The composite event rate of liver outcomes and death in the adult cohort approached 75% and 20% in patients with or without variceal haemorrhage, respectively, with more than half of this incidence happening within the first 6 months.

The researchers summarised that, despite optimal current care, disease progression including variceal haemorrhage, need for liver transplant, and ultimately death is common in both adults and children with portal hypertension. This highlights the urgent need for new medical therapies to improve the prognosis of these patients.

2. Kulkarni S, et al. Portal hypertension secondary to cirrhosis is associated with poor prognosis, irrespective of age and aetiological differences – a large epidemiological study. LB05, UEG Week 2022, 8-11 October, Vienna, Austria.

Chances of transplant-free survival in PSC enhanced by colectomy with ileostomy
Proctocolectomy with permanent ileostomy results in better transplant-free survival in patients with primary sclerosing cholangitis (PSC). This was concluded in a study that found higher chances of survival without liver transplantation for PSC patients who underwent a proctocolectomy with ileostomy compared with those who had no surgery or a colectomy with any kind of remnant colon.

"After transplantation, we know that patients who have undergone a colectomy have decreased rates of recurrent PSC and also a better graft survival," Dr Bregje Mol (Amsterdam UMC, the Netherlands) said [1]. Since the effect of colectomy before transplantation remains unclear to date, Dr Mol and colleagues conducted a retrospective cohort study to explore the effect of proctocolectomy with ileostomy on transplant-free survival in patients with PSC.

"The studies that are available either consist of small patient numbers, don’t take known risk factors into account, or sometimes don’t take colectomy into account as a time-dependent variable," Dr Mol explained. The present study did introduce colectomy as a time-dependent variable. The analysis also corrected for known risk factors like age, sex, concomitant IBD or autoimmune hepatitis, and enrolment in a tertiary centre of care.

The trial enrolled 1,341 adult patients from the EpiPSC2 cohort between 2008 and 2021, leading to over 14,000 patient-years of follow-up. The mean age at PSC diagnosis was 39 years and 36% were women. Most patients had large-duct PSC (86%) and 68% had been diagnosed with IBD. Most of the observed colectomies were indicated by dysplasia/neoplasia or active colitis. During follow-up, the median transplant-free survival was about 19 years.
"We observed 370 liver transplants and almost 400 deaths, of which PSC-related deaths were most common," Dr Mol stated. Comparison between no colectomy, colectomy with remnant colon, or proctocolectomy with ileostomy showed a protective effect of proctocolectomy with ileostomy regarding liver transplantation and PSC-related death (HR 0.47; 95% CI 0.24–0.93; see Figure). For other forms of colectomy with residual colon, no benefit was found. Interestingly, the IBD status of the participants had no impact.

Figure: Results of patients with primary sclerosing cholangitis undergoing no colectomy, colectomy with remnant colon, or proctocolectomy with ileostomy [1]

1. Mol B, et al. Proctocolectomy with permanent ileostomy is associated with better transplant-free survival in patients with primary sclerosing cholangitis: a retrospective cohort study. LB02, UEG Week 2022, 8–11 October, Vienna, Austria.

"In our data, proctocolectomy with ileostomy seems to be associated with a better transplant-free survival, which points towards a role for the colonic microbiota in the disease course of PSC. You only see this effect when you perform a colectomy with ileostomy, so no colonic microbiota can remain, and this effect was not seen with any remnant colon function," Dr Mol concluded.

SARS-CoV-2: Booster doses of key importance for cirrhotic patients

After 2 mRNA vaccine doses against SARS-CoV-2, cirrhotic patients showed significantly reduced T-cell reactivity compared with healthy controls but this was accompanied by lower levels of serum IgG antibodies against the receptor-binding domain of the spike protein. Fortunately, the latter markedly increased after a booster vaccine compared with the second dose and even more following a natural infection.

A previously published meta-analysis showed that patients with liver cirrhosis have an elevated risk for adverse outcomes after a SARS-CoV-2 infection and have a markedly elevated COVID-19-related mortality [1]. Dr Samer Al-Dury ( Sahlgrenska University Hospital, Sweden) and his team explored how well these high-risk patients are protected by vaccination [2]. They determined T cell-mediated and antibody reactivity against the spike 1 (S1) protein of SARS-CoV-2 among 48 cirrhotic patients (of variable aetiologies) and 39 healthy controls after 2 and 3 doses of an mRNA vaccine against SARS-CoV-2.

SARS-CoV-2-specific T-cell reactivity was measured by induced levels of T cell-derived interferon-gamma (IFN-γ) before and after the first and second vaccination with an mRNA vaccine. Moreover, serum IgG antibodies against the receptor-binding domain (RBD) of the spike protein were quantified by immunoassays after the first, second, and third doses of the vaccine.

T-cell reactivity against S1 was significantly reduced in cirrhotic patients compared with healthy controls after the first and second doses of the vaccine (P<0.001 for each comparison). Most (68%) patients lacked detectable S1-specific T-cell reactivity after the first vaccination compared with 19% in controls (P=0.003) and 36% remained without detectable reactivity after the second dose versus 6% in the controls (P=0.009). The lack of T-cell reactivity was mirrored by lower levels of anti-RBD-S1 IgG antibodies after the first (P<0.001) and second (P=0.05 vs controls) vaccination. Impaired T-cell reactivity in cirrhosis remained after correction for potential confounders and was particularly pronounced in patients with advanced cirrhosis. However, anti-RBD-S1 IgG levels increased significantly after the third compared with the second dose. Patients who were vaccinated and had a naturally acquired COVID-19 infection (i.e. hybrid immunity) achieved the best T-cell reactivity, with significantly higher antibody levels compared with those achieved through 3 doses of vaccination alone.

The authors emphasised that in light of immune waning with regards to COVID-19, continued vigilance as well as iterated booster vaccine doses for these vulnerable patients is likely prudent.

Favourable pancreatitis outcomes with procalcitonin-based algorithm to guide antibiotic use

In a single-centre, patient-blinded, randomised-controlled trial, a procalcitonin-based algorithm was successful in sparing both antibiotic use and days of antibiotic use in patients with acute pancreatitis. Despite the markedly reduced use of antibiotics, there was no increase in hospital-acquired infections or harm in patients with acute pancreatitis compared with usual care.

Acute pancreatitis is an inflammatory condition of the pancreas, most commonly caused by bile stones or excessive use of alcohol. In most patients the disease takes a mild course, but in 20–30% it is a life-threatening disease with considerable mortality [1]. International guidelines do not recommend the use of antibiotics in acute pancreatitis in the absence of specific infections [1]. Yet, globally, there is an overuse of antibiotics in all forms of acute pancreatitis, mainly because of the difficulty in clinically distinguishing between a systemic inflammatory response and infection.

Normal physiologic levels of procalcitonin are low, but they rise rapidly in response to infection and fall after eradication. Thus, procalcitonin is a biomarker to distinguish infection from inflammation, and algorithms based on procalcitonin measurement can differentiate bacterial sepsis from a systemic inflammatory response. Therefore, Prof. Ajith Siriwardena (Manchester Royal Infirmary, UK) and his team tested whether a procalcitonin-based algorithm to guide initiation, continuation, and discontinuation of antibiotics can reduce antibiotic use in patients with acute pancreatitis without an adverse effect on outcomes [2].

The PROCAP trial (ISRCTN50584992) included 260 adult patients with acute pancreatitis randomised to either a procalcitonin-based algorithm guiding antibiotic use in addition to usual care (n=132) or usual care only (n=128). Participants had to have at least 2 of the following 3 features: abdominal pain consistent with acute pancreatitis, serum lipase activity (or amylase activity) at least 3 times greater than the upper limit of normal activity, and characteristic findings of acute pancreatitis on contrast-enhanced CT or MRI. Moreover, patients were stratified according to disease severity (mild versus moderately-severe or severe) and admission pathway (either direct admission to the Manchester Royal Infirmary or tertiary transfer from another hospital). If the clinicians wanted to use antibiotics and the procalcitonin level was <1.0 µg/L in the intervention group, it was recommended that no antibiotics were started or patients already treated with antimicrobial therapy should stop it. Only for patients with procalcitonin level ≥1.0 µg/L, an antibiotic intervention was recommended.

Significantly fewer participants in the intervention group used antibiotics compared with the control group (45% vs 62%; P=0.0077). In addition, there were fewer days of antibiotic use in the intervention arm compared with usual care. Regarding the number of clinical infections or hospital-acquired infections, no significant difference was observed between the 2 groups. In addition, mild and severe disease and admission pathways did not influence the results. Overall, costs were markedly reduced by applying the procalcitonin-based algorithm.

“Our findings suggest that procalcitonin-guided care can reduce antibiotic use without increasing infection or harm in patients with acute pancreatitis,” Prof. Siriwardena concluded. Therefore, a procalcitonin-based algorithm should be considered in the care of patients with acute pancreatitis and be incorporated into future guidelines.


Fewer long-term interventions after delayed drainage in necrotising pancreatitis

The comparison of immediate versus postponed drainage in the treatment of necrotising pancreatitis showed no significant benefit for either group in terms of mortality or major complications after 6 months. New
long-term results of the POINTER trial showed similar results at 51 months of follow-up. No statistically significant difference was found in the primary endpoint but delayed drainage continued to result in a lower need for interventions.

In the previously published POINTER trial (ISRCTN33682933), patients with infected necrotic pancreatitis were randomised to an immediate drainage group or a postponed drainage group while being treated with antibiotics [1]. "This trial showed 2 important benefits of postponed intervention at the 6-month follow-up, which is that patients assigned to the postponed drainage group needed fewer interventions when compared with the immediate drainage group and that 35% of the patients were successfully treated with antibiotics only," Ms Noor Sissingh (Leiden University Medical Centre, the Netherlands) explained. On behalf of the Dutch Pancreatitis Study Group, she presented the new POINTER follow-up study that aimed to clarify whether or not long-term results beyond the initial 6 months would uphold these results [2].

Of the 104 patients in the initial trial, 88 patients who were still alive after the initial 6-month follow-up were re-evaluated in the long-term analysis of immediate (e.g. drainage within 24 hours after randomisation once infected necrosis was diagnosed) versus postponed (e.g. drainage that was postponed until the stage of walled-off necrosis was reached) drainage with antibiotics, that defined a composite primary outcome of death or major complications. The baseline characteristics of the initial trial noted no overall differences between the groups. The time between randomisation and drainage was 1 day in the immediate drainage group and 9 days in the postponed drainage group.

The results distinguished between new events (>6 months) and all events within the total follow-up time that extended over a median of 51 months. The results did not show a statistical difference between the 2 drainage schedules for either of the result categories in the primary endpoint, nor in hospital stay or quality-of-life. "Regarding the interventions that were performed after the initial 6 months, you can see that 7 patients in the immediate drainage group needed another drainage procedure after this period, while this was needed for 3 patients in the postponed drainage arm. Also, it is good to mention that 1 of these was a patient that was initially treated with antibiotics only in the POINTER trial," Ms Sissingh stressed.

Compared with all patients receiving drainage per design in the immediate group, only 65% in the postponed group needed drainage, leading to a relative risk of 1.53 (P<0.0001). Moreover, a lower fraction of patients needed a necrosectomy in the postponed drainage group (51% vs 22%; P=0.004). Only in the total follow-up results, the number of interventions was significantly lower in the postponed drainage arm.

Ms Sissingh underlined that even though there were no differences in death or major complications, hospital stay, and quality-of-life, the postponed drainage approach for infected necrotising pancreatitis continued to result in fewer interventions after the initial 6 months follow-up as compared with immediate drainage.


Detection of Europe’s deadliest cancer: much room for improvement

A British analysis of 600 pancreatic cancer cases showed that 46 cases (7.7%) were not detected on imaging scans performed 3 to 18 months prior to diagnosis. An analysis of these cases further revealed that 36.0% were potentially avoidable.

Pancreatic cancer is responsible for 95,000 deaths in the European Union every year and has the lowest survival rate of all cancers in Europe. Life expectancy at the time of diagnosis is just 4.6 months [1]. "There is often only a very short window for curative surgery in pancreatic cancer, meaning it is vital that patients are diagnosed with the disease as early as possible to give them the best chance of survival," said Dr Nosheen Umar (University of Birmingham, UK) [2].

In this retrospective study, Dr Umar and colleagues investigated records of 600 patients diagnosed with pancreatic cancer between 2016 and 2021 to determine whether imaging signs of pancreatic cancer were missed. Pancreatic cancer diagnosed 3 to 8 months after imaging that did not lead to a diagnosis was termed post-imaging pancreatic cancer (PIPC). CT and MRI images were independently reviewed by 2 radiologists to develop an algorithm that categorised the missed cases and identified the most likely explanation for PIPC cases.

The results revealed that 7.7% of the 600 cases were categorised as PIPC and almost half of them were located in the pancreatic head. PIPC were categorised in 5 different
Colorectal Carcinoma: Improving Diagnosis and Therapy

Immunotherapy response may be modulated by microbiome

The PRIMM study explored the dynamics of the gut microbiome during immunotherapy treatment. It revealed that longitudinal gut microbiome profiling of advanced cancer patients may provide insights into the pharmacomicrobiomic interactions associated with the increased success of immune checkpoint blockade (ICB).

Immune checkpoint inhibitors (ICIs) were a huge step forward in oncology. They augment T cell-mediated immune responses to tumours, resulting in improved overall survival of cancer patients at advanced stages in certain types of colorectal cancer. However, durable responses are only achieved by a subset of patients. Recent research has shown that the intestinal microbiome might modulate responses to ICIs [1]. Thus, Dr Johannes Björk (University Medical Center Groningen, the Netherlands) set out to analyse longitudinal changes in the gut microbiome in response to ICB treatment, drawing on data from the observational PRIMM study (NCT03643289).

The researchers profiled the gut microbiome of advanced melanoma patients (n=175) undergoing ICB at cancer centres in the UK and the Netherlands. Shotgun metagenomic sequencing was performed on stool samples to compare the microbiome before and during treatment up to 4 times and to explore the correlation with treatment success, measured in terms of 12-month progression-free survival. The researchers used a regression model with higher-order interactions to estimate how bacterial species and metabolic pathways changed in abundance in different (non-)responder strata from baseline to after the final treatment injection. They also disentangled the longitudinal effect of the following treatment characteristics: the use of single (PD-1) or combination (PD-1 and CTLA-4) ICB, prior exposure to antibiotics or proton pump inhibitors (PPIs), and the effect of immune-related adverse events such as colitis.

The results confirmed that some of the previously reported microbial biomarkers at baseline, such as *Faecalibacterium prausnitzii* and *Bifidobacterium longum*, also increased longitudinally during treatment. However, these associations were often influenced by concomitant treatment characteristics. For example, microbiota differed between single ICB and combination ICB in patients that took no PPIs and no antibiotics. Compared with non-responders, a higher and increasing abundance of butyrate producers from the *Lachnospiraceae* family was identified in responders on single ICB over the entire treatment period. “Of course, this is information that we couldn’t have known from previous baseline predictions alone,” Dr Björk pointed out. In contrast, non-response was associated with a higher and increasing...
abundance of several *Bacteroides* species, some of which have already been identified in non-responders in previous baseline studies.

Dr Björk also emphasised the effect of confounders like PPI or antibiotic use (see Figure). PPI use was associated with a longitudinal increase in *Klebsiella pneumoniae* in non-responders that was not seen in non-responders not taking PPIs. Finally, the researchers compared longitudinal microbiota changes in responders who developed colitis compared with those who did not. In general, immunotherapy-induced colitis resembles the gut microbiome in IBD. *Bacteriodes caccae* was enriched in responders that developed colitis compared with those who did not. Presence of *Faecalibacterium prausnitzii*, also a butyrate producer, was high and stable in responders resistant to colitis compared with those developing colitis.

**Figure: Confounders and outcomes during immunotherapy [2]**

"Microbiome-based interventions should not solely rely on baseline biomarkers. This is key to increasing the efficacy of ICIs. We have to understand the dynamic of the system we want to modulate," Dr Björk concluded.


**Computer-aided colonoscopies improved adenoma detection rates**

Using artificial intelligence (AI) in colonoscopy proved beneficial in terms of higher adenoma detection rates and lower rates of missed adenomas in comparison with the conventional diagnostic procedure. The computer-aided detection was particularly helpful in the discovery of small and very small adenomas.

"Up to a fourth of all adenomas are missed during colonoscopy, which potentially results in post-colonoscopy colorectal cancers," Dr Michiel Maas (Raboud UMC, the Netherlands) said [1]. To further explore possibilities to improve this situation, Dr Maas and colleagues designed an international, multicentre, randomised-tandem trial to evaluate the potential enhancement of polyp detection by using AI in colonoscopy. In 2 different groups, 916 patients with a mean age of about 60 years underwent a colonoscopy with or without use of the MAGENTIQ-COLO™ study device (magentiq.com). "A subset of patients was further randomised to undergo a tandem colonoscopy, so either a conventional colonoscopy followed by AI colonoscopy or vice versa," Dr Maas explained. The primary outcome measure was adenoma per colonoscopy (APC). Secondary objectives were the adenoma detection rate (ADR) and adenoma miss rate. Reasons for the colonoscopy in the conventional group and computer-aided detection group were surveillance (44.2% and 43.1%, respectively) and non-immunological faecal occult blood test (55.8% and 56.9%, respectively).

The results showed a statistically significant APC rate for the computer-aided detection compared with the conventional group (0.70 vs 0.51; P=0.014). The ADR was also superior with computer-aided detection; not only in the entire cohort (37% vs 30%; P=0.014) but also for both indications: surveillance (P=0.001) and non-immunological faecal occult blood test (P=0.014). Dr Maas conveyed that the adenoma miss rate was almost halved with computer-aided detection (19%) in comparison with conventional colonoscopy (36%), while withdrawal times without intervention were equal in both groups.

In terms of adenoma characteristics that aided in better detection with computer-aided detection, size mattered. "We found an increased detection of diminutive adenomas sized ≤5 mm, but we also found an increase in small adenomas sized 6–9 mm in the computer-aided detection group compared with the conventional group. There were no differences in the detection of advanced adenomas or sessile serrated lesions," Dr Maas stated. Furthermore, computer-aided detection found more adenomas in the proximal colon (P=0.006).

"This study further emphasises the beneficial role of AI or computer-aided detection in improving our detection rates in a regular screening and surveillance population," Dr Maas concluded.

Benefit of colon cancer screening with colonoscopy lower than anticipated

A one-time screening colonoscopy reduced the risk of incident colorectal cancer (CRC) by 18% compared with no endoscopic screening. Also, at 10 years, no significantly reduced mortality was detected with or without colonoscopy screening in the NordICC trial.

Screening by colonoscopy is common in many European countries and North America [1]. “However, no randomised trials up to today have been available to quantify the benefits of this screening test for CRC and, therefore, we do not really know how effective it is in terms of the important endpoints of incidence and mortality of CRC,” Prof. Michael Bretthauer (Oslo University, Norway) explained the motivation for the randomised-controlled NordICC trial (NCT00883792). NordICC is the first, randomised, population-based trial to investigate the effect size that CRC screening by colonoscopy has on the incidence and mortality of CRC [1,2]. This magnitude of effect is important not only on an individual level for shared decision-making with a patient but also for the planning of official screening programmes.

The study enrolled 95,000 healthy people between 55 and 64 years of age directly from population registries in the partaking countries of Norway, Poland, Sweden, and the Netherlands. Participants were randomised to either receive an invitation for 1 colonoscopy screening or usual care, which meant no screening in the trial countries. Of the invitees, 42% participated in a colonoscopy. The presented analysis of the 10-year results could not include the 9,780 patients from the Netherlands due to Dutch General Data Protection Regulations.

“In terms of screening performance, it went very well: there was good bowel preparation for the vast majority of the patients; caecal intubation rate exceeded 95%,” Prof. Brethauer commented on the participant’s characteristics. The screening colonoscopies did not lead to any deaths or perforations and all 15 cases of major bleeding could be managed endoscopically.

In the intention-to-treat population, the result for the primary endpoint of CRC incidence after 10 years revealed a cumulative CRC risk of 1.20% in those without screening compared with 0.98% in those in the invited group. This resulted in a risk ratio (RR) of 0.82 (95% CI 0.70–0.93) or a risk reduction of 18% with screening. Prof. Brethauer also presented the results of an adjusted per-protocol analysis, which he emphasised are not as trustworthy as those from the intention-to-treat population. “But they are still informative, because what you do, or try to do, is to estimate the effect if everybody had accepted the screening,” he explained. The per-protocol assessment showed an incidence of 1.22% on usual care and 0.84% with colonoscopy screening, leading to a risk reduction of 31% (RR 0.69; 95% CI 0.55–0.83).

As for the secondary endpoint of CRC mortality, the difference between both intention-to-treat groups was low: 0.31% (usual care) versus 0.28% (invited group) with a non-significant risk reduction of 10% (RR 0.90; 95% CI 0.64–1.16). In his summary, Prof. Brethauer further added that with regard to all-cause mortality, there was no difference between the 2 groups.


Screening-detected colorectal cancers may have superior surgical outcomes

When comparing post-operative 90-day mortality with surgical and non-surgical outcomes, patients whose colorectal cancer (CRC) was found in the Danish screening programme were at a surgical advantage. However, looking at the subgroups according to Union for International Cancer Control (UICC) stages, benefits were only present in UICC 3 and 4.

Denmark has implemented a screening programme for CRC [1]. “We know that it leads to a lower stage at the time of diagnosis, but current evidence is sparse and not agreeing on the effect on the surgical outcome,” Dr Jannie Dressler (Bispebjerg Hospital, Denmark) explained the reason for the retrospective, nationwide, register-based cohort study. The analysis evaluated the potential differences in risks involved for patients who were diagnosed with CRC between January 2014 and March 2018.

The study cohort included 10,606 adults aged 50–75 years who received surgery for their CRC. Among them were 4,497 participants whose diagnosis was detected through screening (SD-CRC) and 6,109 who did not partake in the programme (NSD-CRC). The 2 groups were significantly heterogeneous in numerous disease and tumour-related factors. The analysis was adjusted for 5-year age groups, sex, cancer type, and Charlson comorbidity index.
Significant outcomes in favour of the SD-CRC group were detected for surgical as well as non-surgical complications (both \( P<0.0001 \)). SD-CRC participants received significantly fewer blood transfusions, had fewer tumour perforations, their time in hospital was shorter, and the 90-day mortality rate was lower than in the NSD-CRC group (\( P<0.0001 \) for all comparisons).

The picture changed regarding the 90-day mortality rate, surgical complications, and non-surgical complications after stratification according to UICC stages of the CRC. In UICC stages 1 and 2, the differences were no longer significant. In UICC 3, the outcomes for 90-day mortality and surgical complications remained significantly different (\( P=0.029 \) and \( P=0.005 \)). In UICC 4, this was the case for non-surgical complications in addition to the 90-day mortality rate (\( P=0.020 \) and \( P<0.0001 \)).

Dr Dressler stressed that these findings are important for various reasons, including as argument for the continuation and improvement of the CRC screening programme, for better participation rates, and also for CRC screening programme implementation in other countries. “And it is really important when you want to inform your patient about the prognosis,” she finally underlined in her conclusion.