Medicom International Conference Series in Gastroenterology

17th Congress of ECCO

European Crohn's and Colitis Organisation

16–19 FEBRUARY 2022

PEER-REVIEWED CONFERENCE REPORT

U-ACHIEVE Achieved

The 52-week results of the phase 3 U-ACHIEVE trial showed that upadacitinib maintenance therapy sustained improvements in abdominal pain, bowel urgency, and fatigue in participants with ulcerative colitis.

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Is Subcutaneous Infliximab Better Than Vedolizumab?

Infliximab therapy outperformed vedolizumab therapy in participants with Crohn's disease in a head-to-head analysis, although for colitis, the 2 therapies appeared to be equally efficacious.

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New Classifications For Perianal Fistulising Crohn's Disease

A new patient-oriented classification system for perianal fistulising Crohn's disease includes treatment suggestions per class and patient-specific recommendations for clinical trial suitability.

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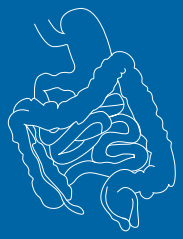

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Letter from the Editor

photo: Janne van de Weijer, blue office battery

Dear colleagues,

Unfortunately, due to COVID-19 restrictions, ECCO (European Crohn's and Colitis Organisation) 2022 was for the second time an online event.
The theme of this year was "Navigating the Oceans of IBD", with tantalizing topics such as "Developing environment recipes for IBD", "Keeping the patient at home: Is telemedicine the future?", "Aiming high with treatment goals in IBD: The modern Icarus?" and 'Do we see light at the end of the fistula track".

Although COVID-19 has had a major impact on our daily lives, the quality of IBD research has not been affected. It is a great honour to present this ECCO 2022 Medicom Conference Report in which we cover amongst others updates on new therapies, head-to-head comparisons and insights into specific therapeutic strategies.

I hope you enjoy it and am looking forward to meeting you in person next year in Copenhagen.

Yours, sincerely
Marjolijn Duijvestein

Biography
Dr Marjolijn Duijvestein works as a gastroenterologist in the IBD team of the Radboudumc in Nijmegen, the Netherlands. In 2012 she obtained her PhD at Leiden University and was trained as a gastroenterologist specialised in IBD disease at the Amsterdam UMC in Amsterdam. As part of her training, she gained experience at the University of California San Diego (UCSD, USA) and performed an internship at Alimentiv (former Robarts Clinical Trials), an academic research organisation dedicated to drug development for IBD. Her clinical activity and research are focused on IBD, in particular clinical and translational research.

Conflict of Interest Statement:
She has served as an advisor for Echo pharma and Robarts Clinical Trials, reports nonfinancial support from Dr Falk Pharma, and received speaker fees from Janssen, Merck & Co., Pfizer, Takeda and Tillotts Pharma. Advisory boards Janssen, Takeda, BMS and Abbvie.

Novel Treatment Modalities

Guselkumab shows encouraging safety and efficacy in ulcerative colitis

Guselkumab induction therapy was superior to placebo across key endpoints in patients with moderately to severely active ulcerative colitis (UC) in the phase 2b QUASAR trial. Moreover, the results showed a favourable safety profile of guselkumab in the study population.

Guselkumab is an IL-23 inhibitor, approved for the treatment of psoriatic arthritis and psoriasis, and currently under investigation as a therapy for patients with inflammatory bowel disease (IBD), explained Prof. Axel Dignass (Agaplesion Markus Hospital, Germany) [1]. The double-blind, placebo-controlled, phase 2b QUASAR Induction Study 1 (NCT04033445) randomised 313 patients with moderately to severely active UC, who failed on conventional or advanced therapies, 1:1:1 to intravenous 400 mg guselkumab, 200 mg guselkumab, or placebo every 4 weeks. The primary endpoints were clinical response[a] and clinical remission[b] at week 12.

The proportion of patients achieving clinical response at week 12 were significantly higher in the guselkumab 400 mg arm (60.7%) and the guselkumab 200 mg arm (61.4%) as compared with placebo (27.6%; P<0.001). The proportion of patients in clinical remission at week 12 confirmed the superiority of guselkumab (400 mg 25.2%; 200 mg 25.7%) over placebo (9.5%; P<0.05) in this study population. Furthermore, secondary endpoints at week 12 demonstrated efficacy benefits of guselkumab (combined arms) over placebo, including symptomatic remission[c] (49.0% vs 20.0%; P<0.001), endoscopic improvement[d] (30.8% vs 12.4%; P<0.001), histo-endoscopic mucosal improvement[e] (23.6% vs 8.6%; P<0.001), and endoscopic normalisation[f] (15.9% vs 6.7%, P<0.05).

Guselkumab was well tolerated in this patient population and no notable differences in key safety events were reported between the low-dose and high-dose guselkumab arms. No significant difference was detected in the occurrence of adverse events (AEs) between participants who received placebo (55.2%) and participants who received guselkumab (46.2%). Serious AE proportion was higher in the placebo arm (5.7%) than in the combined guselkumab arms (1.0%). Importantly, the proportion of infections were comparable across groups (placebo 11.4% vs guselkumab 10.6%).

Prof. Dignass added that no dose response was observed for guselkumab. He mentioned that it could be that the lower dose of guselkumab (200 mg) is already the optimal dose for these patients, but further analyses need to be performed to clarify this point.

a. *Clinical response is defined as decrease from induction baseline in de modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore of 0 or 1.*
b. *Clinical remission is defined as stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.*
c. *Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.*
d. *Endoscopic improvement is defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.*
e. *Histo-endoscopic mucosal improvement is defined as achieving a combination of histologic improvement (neutrophil infiltration in <5 percent of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system) and endoscopic improvement.*
f. *Endoscopic normalisation is defined as an endoscopy subscore of 0.*

1. Dignass A, et al. The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active Ulcerative Colitis: Phase 2b QUASAR Study results through week 12. OP23, ECCO 2022, 16–19 February.

Guselkumab maintenance therapy achieved high efficacy rates in Crohn's disease

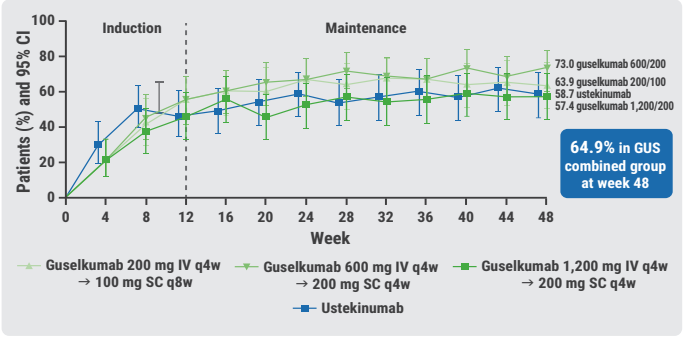
Subcutaneous guselkumab maintenance therapy achieved high efficacy rates in participants with Crohn's disease (CD) after 2 years of follow-up in the treat-through, phase 2 GALAXI-1 study. The safety profile was favourable in this population and consistent with the safety profile of guselkumab in approved indications. Phase 3 studies assessing guselkumab in CD are currently running.

The phase 2 GALAXI-1 trial (NCT03466411) randomised participants with moderately to severely active CD, who failed on prior conventional and/or biologic therapies, to 200 mg guselkumab, 600 mg guselkumab, 1,200 mg guselkumab, or placebo (intravenous, every 4 weeks). The results from the 12-week induction study demonstrated that guselkumab is associated with significantly improved clinical outcomes compared with placebo, according to Prof. Silvio Danese (Vita-Salute San Raffaele University, Italy) [1]. After week 12, participants in the 1,200 mg and 600 mg arms received 200 mg guselkumab, subcutaneous, every 4 weeks (n=61; n=63), whereas participants who were originally randomised to 200 mg guselkumab, received 100 mg guselkumab, subcutaneous,

every 8 weeks (n=61). In addition, an ustekinumab reference arm was included (90 mg subcutaneous, every 8 weeks; n=63). At ECCO 2022 the 48-week results were presented, in which the placebo arm was not included.

Of the participants on guselkumab, 64.9% achieved clinical remission[a] through week 48 (see Figure), as compared with 58.7% in participants treated with ustekinumab. In addition, corticosteroid-free clinical remission[b] proportions ranged between 55.7% and 71.4% in the guselkumab arms and was 58.7% in the ustekinumab arm. Similarly, Patient Reported Outcome (PRO-2) remission[c] at week 48 was achieved by 50.8%– 69.8% of the participants treated with guselkumab and 46.0% of the participants treated with ustekinumab.

Figure: Participants in clinical remission through week 48 [1]



The proportion of serious adverse events (AEs) was 7.3% for the combined guselkumab arms and 12.7% for the ustekinumab arm. No opportunistic infections, cases of tuberculosis, or deaths were reported in any study group.

Prof. Danese mentioned that the current study was not powered to directly compare the different guselkumab arms in terms of efficacy. He also emphasised that the ustekinumab arm was a reference arm only. He expects guselkumab to be superior to ustekinumab in patients with CD, since the mechanism of action of guselkumab is more specific. However, a direct comparison needs to be performed between the 2 agents to prove this.

a. Clinical remission is defined as a Crohn's Disease Activity Index (CDAI) score <150.

b. Corticosteroid-free clinical remission is defined as a CDAI score <150 at week 48 and not receiving corticosteroids at week 48.

c. PRO-2 remission is defined as the unweighted CDAI component of daily abdominal pain score ≤1, and the unweighted CDAI component of daily average stool frequency score ≤3, and no worsening of abdominal pain or stool frequency from baseline.

1. Danese S, et al. Clinical efficacy and safety of guselkumab maintenance therapy in patients with moderately to severely active Crohn's Disease: Week 48 analyses from the phase 2 GALAXI 1 study. OP24, ECCO 2022, 16–19 February.

Mirikizumab efficacious for active ulcerative colitis

Mirikizumab was more efficacious than placebo as induction therapy for participants with moderately to severely active ulcerative colitis (UC). In addition, mirikizumab showed a favourable safety profile. These results from the phase 3 LUCENT-1 trial support the applicability of mirikizumab in patients with UC.

Mirikizumab is an IgG4 monoclonal antibody targeting IL-23. In a phase 2 study (NCT02589665), this agent outperformed placebo in participants with active UC. The multicentre, double-blind, phase 3 LUCENT-1 trial (NCT03518086) randomised participants with moderately to severely active UC, who failed on at least 1 prior therapy, to mirikizumab (n=868) or placebo (n=294). Participants in the experimental arm received 300 mg mirikizumab intravenous, at weeks 0, 4, and 8. Clinical remission[a] at week 12 was the primary endpoint of this study. Prof. Geert D'Haens (Amsterdam University Medical Center, the Netherlands) presented the results [1].

At week 12, the clinical remission rate was significantly higher in the mirikizumab arm (24.2%) than in the placebo arm (13.3%; P=0.00006). Mirikizumab showed a benefit with regard to clinical remission in the subset of participants who were naïve to biologic therapy versus placebo (30.9% vs 15.8%; P<0.001). In patients who failed on a previous biologic therapy, the numerical benefit in clinical remission rate of patients on mirkizumab over patients on placebo was not significant (15.2% vs 8.5%; P=0.065). Furthermore, mirikizumab outperformed placebo on all key secondary endpoints, including clinical response[b] (63.5% vs 42.2%; P<0.00001), endoscopic remission[c] (36.3% vs 21.1%; P<0.00001), histologic-endoscopic mucosal improvement[d] (27.1% vs 13.9%; P<0.00001), and bowel urgency (least square mean difference for urgency numerical rating scale from baseline versus placebo = -1; P<0.00001). Notably, 4 weeks after treatment initiation, mirikizumab receivers already demonstrated a significant improvement in symptomatic remission compared with placebo receivers.

The safety analysis did not display unexpected safety issues of mirikizumab therapy. Treatment-related adverse events occurred in 46.1% of the participants in the placebo arm and in 44.5% of the participants in the mirikizumab arm. Serious adverse events were numerically more frequently reported in the placebo arm (5.3% vs 2.8%).

Prof. D'Haens argued that post-hoc analyses and head-to-head studies are needed to determine the position of mirikizumab in the treatment sequencing of patients with UC. He speculated that IL-23 inhibition may be more specific than combined IL-12 and IL-23 inhibition, which is the mechanism of action of ustekinumab. However, this needs to be investigated in a direct comparison between ustekinumab and mirikizumab.

a. Clinical remission is defined as stool frequency subscore of 0 or 1 with a ≥1-point decrease from baseline, and rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1 excluding friability.

b. Clinical response is defined as a decrease in the modified Mayo score of ≥2 points and ≥30% decrease from baseline, and a decrease of ≥1 point in the rectal bleeding subscore from baseline, or a rectal bleeding score of 0 or 1.

c. Endoscopic remission is defined as an Endoscopic subscore of 0 or 1 excluding friability.

d. Histologic-endoscopic mucosal improvement isdefined as histologic improvement, defined as Geboes scoring system with neutrophil infiltration in <5% of crypts, no crypts destruction, and no erosions, ulcerations, or granulation tissue.

1. D'Haens G, et al. Efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active Ulcerative Colitis: Results from the Phase 3 LUCENT-1 study. OP26, ECCO 2022, 16–19 February.

Risankizumab more efficacious in colonic than in ileal Crohn's disease

A post-hoc analysis of the phase 3 ADVANCE, MOTIVATE, and FORTIFY trials assessing risankizumab in participants with Crohn's disease (CD) confirmed the efficacy of induction and maintenance therapies with this agent. The analysis further showed that risankizumab therapy is more efficacious in participants with CD who had colonic involvement than in those who had ileal involvement.

Risankizumab is an IL-23 inhibitor under investigation for the treatment of patients with CD. Although several phase 3 trials have demonstrated the safety and efficacy of risankizumab as intravenous induction therapy and subcutaneous maintenance therapy in patients with CD, the efficacy of this therapy regarding disease location has not yet been investigated. "And we know that disease location may affect treatment outcomes of biologic therapies in CD," explained Dr Peter Bossuyt (Imelda General Hospital, Belgium) [1,2]. Therefore, the current, post-hoc analysis used the data of the phase 3 ADVANCE (NCT03105128), MOTIVATE (NCT03104413), and FORTIFY (NCT03105102) trials to analyse the efficacy of risankizumab according to disease location [2].

Clinical remission[a] at week 12 was higher in participants with colonic involvement (54.3%; n=190; P<0.001) and participants with ileal-colonic involvement (39.7%; n=252; P<0.001) who received risankizumab induction therapy compared with participants who received placebo (23.8% and 20.7%, respectively). In participants with ileal disease (n=85), a benefit of risankizumab was seen over placebo (33.7% vs 22.2%), although not significant. Similar results were reported for endoscopic responses[b] and endoscopic remission[c] at week 12.

Furthermore, risankizumab maintenance therapy significantly outperformed placebo in participants with colonic (54.0% [n=59] vs 37.1% [n=62]; P<0.05) or ileal-colonic involvement (53.3% [n= 67] vs 40.5% [n=79]; P<0.05), but not ileal disease (40% [n=15] vs 52.2% [n=23]), with regard to clinical remission at week 52. Dr Bossuyt added that endoscopic response, a more objective endpoint, did show benefits of risankizumab compared with placebo in participants with ileal disease (26.7% [n=15] vs 8.7% [n=23]). The number of participants with ileal disease in the maintenance analysis was low (n=38), thus these results should be interpreted with caution.

"This study confirms the efficacy of risankizumab in patients with moderately to severely active CD and confirms greater improvements in patients with colonic involvement," said Dr Bossuyt. "Unfortunately, the treatment success is lower in participants with ileal disease, a pattern we have seen for other molecules as well. I believe that these results show us that we must recognise ileal and colonic Crohn's disease as 2 separate conditions, extending beyond the difference in disease location."

a. Clinical remission is defined as a Crohn's Disease Activity Index (CDAI) >150.

b. Endoscopic response is defined as a >50% decrease from baseline in SES-CD, or a 2-point reduction from baseline for patients with ileal disease and baseline SES-CD of 4.

c. Endoscopic remission was defined as a SES-CD ≤4 and at least a 2-point reduction vs baseline with no subscore greater than 1 in any individual variable.

1. Rivière P, et al. Am J Gastroenterol. 2021;116(1):134–141.
2. Bossuyt P, et al. Efficacy of risankizumab induction and maintenance therapy by baseline Crohn's Disease location: Post hoc analysis of the phase 3 ADVANCE, MOTIVATE, and FORTIFY studies. OP40, ECCO 2022, 16–19 February.

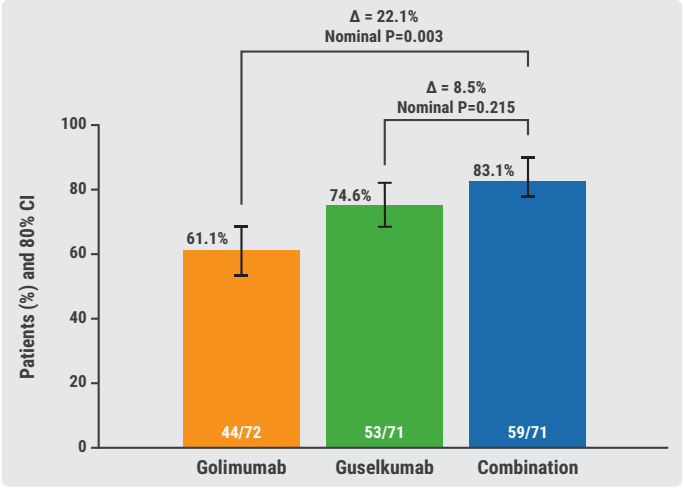
Guselkumab plus golimumab promising combination for ulcerative colitis

The combination of guselkumab and golimumab resulted in improved clinical outcomes in participants with active ulcerative colitis (UC) compared with either guselkumab or golimumab monotherapy in a phase 2 study. Moreover, the safety profiles were similar across treatment groups. Further trials are warranted to evaluate the safety and efficacy of this promising combination regimen in patients with UC.

Preclinical data from a murine model of acute colitis has suggested that the combination therapy of guselkumab, an IL-23 inhibitor, and golimumab, a TNF inhibitor, may lead to improved outcomes in patients with UC [1]. A phase 2, proof-of-concept study (NCT03662542) was conducted to assess the efficacy and safety of guselkumab plus golimumab compared with guselkumab or golimumab monotherapy in participants with moderately to severely active UC [2]. Participants (n=214) were randomised 1:1:1 to golimumab monotherapy (subcutaneous 200 mg at week 0, 100 mg at weeks 2, 6, and 10), guselkumab monotherapy (intravenous 200 mg at weeks 0, 4, and 8), or a combination of these 2 regimens (200 mg guselkumab intravenous plus 200 mg golimumab subcutaneous at week 0, 100 mg golimumab subcutaneous at weeks 2, 6, and 10, 200 mg guselkumab intravenous at week 4 and 8). The primary outcome was the clinical response[a] at week 12. Prof. Bruce Sands (Mount Sinai School of Medicine, NY, USA) presented the results.

At week 12, the combination therapy significantly outperformed golimumab monotherapy (83.1% vs 61.1%; P=0.003) but not guselkumab monotherapy (83.1% vs 74.6%; P=0.215) regarding clinical response rates (see Figure). Clinical remission[b] was significantly higher in the combination therapy arm (36.6%) compared with guselkumab alone (21.1%; P=0.041), and borderline significant compared with golimumab alone (22.2%; P=0.058). Furthermore, endoscopic improvement[c] significantly favoured the combination therapy over the monotherapy arms (P=0.003 for combination vs golimumab; P=0.016 for combination vs guselkumab) whereas for histologic remission[d] the combination therapy was only significantly higher than golimumab monotherapy (P=0.003).

Figure: Clinical response of guselkumab, golimumab, or the combination at week 12 [2]



The safety profiles of the 3 treatment regimens were similar. Adverse events (AEs) occurred in 52.8%, 43.7%, and 40.8% of the participants in the golimumab, guselkumab, and combination therapy arm, respectively. Corresponding proportions of serious AEs were 1.4%, 2.8%, and 1.4%. The proportion of infections did not differ between the treatment conditions, with 14.1% of the participants in the golimumab or combination therapy arm and 22.2% of the participants in the golimumab arm displaying an infection. No deaths, malignancies, or opportunistic infections were observed at week 12.

"Combination induction treatment with guselkumab plus golimumab resulted in greater proportions of patients achieving a clinical response, clinical remission, endoscopic improvement and normalisation, and the composite endpoint of histologic remission and endoscopic improvement at week 1," concluded Prof. Sands. "Further study of this combination therapy is warranted."

a. Clinical response is defined as a decrease in the Mayo score ≥30% and ≥3 points, with either a decrease in rectal bleeding subscore ≥1 or rectal bleeding subscore of 0 or 1.

b. Clinical remission is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on endoscopy, where the stool frequency subscore has not increased from baseline.

c. Endoscopic improvement is defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

d. Histologic remission is defined as absence of neutrophils of the mucosa, no crypts destruction, and no erosion, ulcerations, or granulation tissues according to the Geboes grading system.

1. Perrigoue J, et al. In silico evaluation and pre-clinical efficacy of anti-TNF and anti-IL-23 combination therapy in Inflammatory Bowel Disease. P328, ECCO 2022, 16–19 February.
2. Sands BE, et al. Efficacy and safety of combination induction therapy with guselkumab and golimumab in participants with moderately-to-severely active Ulcerative Colitis: Results through week 12 of a phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept study. OP36, ECCO 2022, 16–19 February.

Combined endpoint may support personalised medicine in ulcerative colitis

A combined clinical, biological, health-related quality of life, and endoscopic endpoint displayed improvements for participants with ulcerative colitis (UC) treated with filgotinib compared with placebo. In addition, the novel endpoint was strongly associated with general quality-of-life measures. Holistic assessments of participants via a combined endpoint are useful to identify super responders and may support personalised medicine.

Prof. Stefan Schreiber (Christian-Albrecht University, Germany) argued that traditional outcomes do not consider the comprehensiveness of the individual patients' experience. Holistic assessments may help to identify patients in whom

therapies demonstrate the largest effect and lead to disease control [1]. A combined endpoint was evaluated in the 200 mg filgotinib and placebo arms of the SELECTION trial (NCT02914522), a phase 2b/3 study that tested filgotinib in participants with UC. The combined endpoint was defined as achieving all of the following:

- clinical remission: partial Mayo score ≤2 and no subscore >1 (excluding endoscopy subscore);
- biologic remission: faecal calprotectin <150 µg/g;
- endoscopic improvement: Mayo endoscopic score of 0 or 1; and
- health-related quality-of-life: Inflammatory Bowel Disease questionnaire >170.

In the biologic-naïve filgotinib arm (n=245), 17.6% of the participants achieved the combined endpoint compared with 4.4% in the placebo arm (n=136; P<0.001). In the biologic-experienced cohort (n=260), the corresponding rates were 4.6% and 1.4% (n=141 for placebo arm; P=0.167). In addition, the combined endpoint displayed that improvements achieved during induction therapy were sustained during maintenance therapy (filgotinib 22.1% vs placebo 7.1%; P=0.002). Furthermore, participants who achieved the combined clinical endpoint were more likely to show higher minimal clinically important difference (MCID) improvements, the smallest change in measurement that signifies an important improvement, on physical and mental subscales of the 36-Item Short Form Survey (SF-36) and the EuroQol 5 Dimensions (EQ-5D) measure.

Prof. Schreiber argued that the low rate of participants who achieved the combined endpoint indicates that existing treatments need to be optimised. "Also, future studies should investigate the optimal components of a combined endpoint, characterise the trajectories of patients achieving this endpoint, and identify predictors of early and deep responses to therapy. In this way, combined endpoints may help to improve outcomes for our patients with UC."

1. Schreiber S, et al. Exploring disease control by combining clinical, biological, and health-related quality of life remission with endoscopic improvements among Ulcerative Colitis patients treated with filgotinib: A post-hoc analysis from the SELECTION trial. OP07, ECCO 2022, 16–19 February.

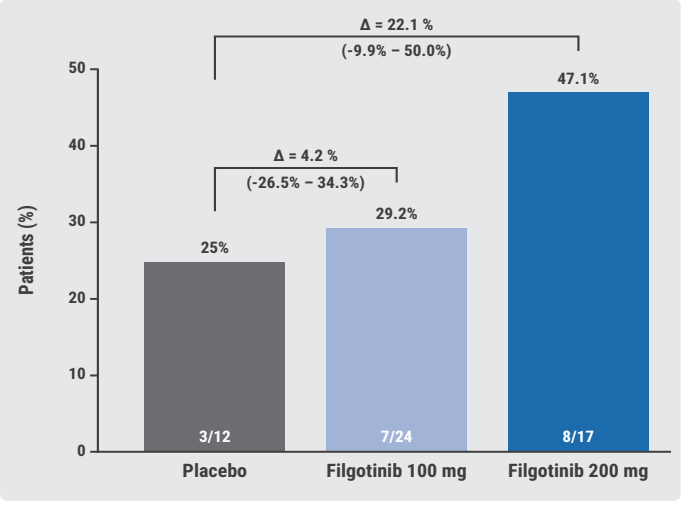
Filgotinib seems promising for perianal fistulising Crohn's disease

Filgotinib was associated with numerically higher response rates than placebo in participants with perianal fistulising Crohn's disease (PFCD). In addition, the agent was well tolerated in this participant population. Further studies are warranted to confirm the encouraging results of the current, phase 2 DIVERGENCE 2 study, which was underpowered due to low enrollment during the COVID-19 pandemic.

Dr Walter Reinisch (Medical University of Vienna, Austria) explained that infliximab is the only agent with demonstrated efficacy for participants with PFCD in randomised, placebo-controlled trials [1]. The current, double-blind, placebo-controlled, phase 2 DIVERGENCE 2 trial (NCT03077412) investigated the efficacy and safety of filgotinib in participants with PFCD. Filgotinib is a once-daily, oral JAK inhibitor, approved for the treatment of active UC. Participants with PFCD, who failed at least 1 prior therapy, were randomised to 100 mg filgotinib (n=25), 200 mg filgotinib (n=17), or placebo (n=15). The primary endpoint was combined fistula response[a] at week 24.

The primary endpoint displayed higher proportion of response for participants in the filgotinib 200 mg arm over placebo (47.1% vs 25%). The combined fistula response in the filgotinib 100 mg arm was 29.2% (see Figure). In addition, the median time to fistula response was shorter in the filgotinib 200 mg arm compared with the placebo arm (15.0 vs 35.5 days), although not significantly different.

Figure: Combined fistula response at week 24 [1]



Dr Reinisch added that filgotinib was in general well tolerated in this participant population. The proportion of treatment-related adverse events was slightly higher in the filgotinib 200 mg arm than in the placebo arm (82.4% vs 73.3%). Also, the proportion of infections was higher in participants receiving 200 mg filgotinib than in participants receiving placebo (64.7% vs 53.3%), but not significant.

"Since limited treatment options are available, PFCD is still a challenging condition that reduces patients' quality of life. Although the study was underpowered due to limited enrollments during the COVID-19 pandemic, the promising results of this study warrant further investigation of filgotinib in patients with PFCD," concluded Dr Reinisch.

a. Combined fistula response is defined as the reduction of ≥1 from baseline in the number of draining external perianal fistula openings and absence of fluid collection of >1 cm on MRI.

1. Reinisch W, et al. Efficacy and safety of filgotinib for the treatment of perianal fistulizing Crohn's Disease: Results from the phase 2 DIVERGENCE 2 study. OP18, ECCO 2022, 16–19 February.

Upadacitinib maintenance therapy delivers sustained improvements in active ulcerative colitis

Upadacitinib maintenance therapy was associated with sustained improvements in abdominal pain, bowel urgency, and fatigue in participants with moderately to severely active ulcerative colitis (UC) who responded to upadacitinib induction therapy. These are the 52-week results of the phase 3 U-ACHIEVE maintenance trial.

The U-ACHIEVE induction (NCT02819635) and U-ACCOMPLISH (NCT03653026) trials showed that induction therapy with the JAK inhibitor upadacitinib (45 mg, once daily) resulted in significant improvements in abdominal pain, bowel urgency, and fatigue in participants with active UC who relapsed or were refractory to a previous conventional or biologic therapy [1,2]. Prof. Silvio Danese (Vita-Salute San Raffaele University, Italy) presented the 52-week results of the the U-ACHIEVE maintenance study, including 451 participants who achieved clinical remission on upadacitinib induction therapy [3]. Participants were randomised to upadacitinib 30 mg, once daily (n=154), upadacitinib 15 mg, once daily (n=148), or placebo (n=149). The clinical endpoints were patient self-reported abdominal pain, bowel urgency, and fatigue.

At week 52, participants receiving upadacitinib maintenance therapy were significantly more likely to report no abdominal pain than participants receiving placebo (15 mg 45.9%; 30 mg 55.3%; placebo 20.8%; P<0.001). Similarly, a significantly greater proportion of participants in the upadacitinib arms did not demonstrate bowel urgency (15 mg 56.1%; 30 mg 63.6%) compared with participants in the placebo arm (17.4%; P<0.001). In addition, fatigue was less common in the upadacitinib groups, as was displayed by a >40 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) score (15 mg 52.0%; 30 mg 55.7%; placebo 35.7%; P<0.01).

"The results of this trial were promising, but based on a double-blind, randomised, placebo-controlled study. Therefore, the results may not reflect quality-of-life benefits of upadacitinib in the real-world setting," concluded Prof. Danese.

1. Sandborn WJ, et al. Gastroenterology. 2020;158(8):2139-2149.
2. Vermeire S, et al. J Crohns Colitis. 2021;15(Suppl1):S021-S022.
3. Danese S, et al. The effects of maintenance therapy with upadacitinib on abdominal pain, bowel urgency, and fatigue in patients with moderately to severely active Ulcerative Colitis: Phase 3 U-ACHIEVE maintenance results. OP08, ECCO 2022, 16–19 February.

Upadacitinib counters extraintestinal manifestations in ulcerative colitis

Upadacitinib was more effective than placebo in resolving extraintestinal manifestations (EIMs) in participants with ulcerative colitis (UC) in a phase 3 trial. Induction therapy with upadacitinib initiated the resolution of EIMs, whereas maintenance therapy elicited further improvements. A higher maintenance dose was associated with greater gains than a lower maintenance dose.

EIMs are frequently observed in patients with UC. In addition, these EIMs are challenging to treat and may reduce the quality of life for patients with UC. Since the JAK inhibitor upadacitinib was demonstrated to be safe and efficacious in patients with UC, Prof. Jean-Frédéric Colombel (Icahn School of Medicine at Mount Sinai, NY, USA) aimed to evaluate the impact of upadacitinib on EIMs in participants with moderately to severely active UC [1–4]. Data was included from the phase 3 U-ACHIEVE induction and maintenance trials (NCT02819635) and U-ACCOMPLISH induction trial (NCT03653026).

Peripheral arthropathy, axial arthropathy, and anaemia were the most common EIMs in this population. Data from the induction studies showed that 8 weeks of therapy with 45 mg upadacitinib (n=660) was associated with higher proportions of achieving resolution of EIMs compared with placebo (n=328) (40.0% vs 33.3%). For arthropathies, the corresponding figures were 54.7% and 42.1%. In addition, anaemia was resolved in 38.2% of the participants in the upadacitinib arms and 32.6% of the participants in the placebo arms after 8 weeks of therapy. None of these differences were significant.

At week 52, maintenance therapy with 30 mg upadacitinib (n=154) significantly outperformed placebo (n=149) in the resolution of EIMs (65.9% vs 24.3%; P<0.001). However, 15 mg upadacitinib maintenance therapy (n=148) had no significant benefit over placebo in the resolution of EIMs (41.7% vs 24.3%). Similarly, resolution of arthropathies was significantly more likely to occur in participants in the

30 mg arm compared with participants in the placebo arm (66.7% vs 22.2%; P=0.010), whereas participants in the 15 mg arm showed no significant benefit over placebo (38.5%). Furthermore, in 70.8% of the participants in the 30 mg arm, anaemia was resolved at week 52, compared with 36.4% in the placebo arm (P=0.019). Anaemia was resolved in 50.0% of the participants in the 15 mg arm, but this was not significantly different from placebo (36.4%).

1. Sandborn WJ, et al. Gastroenterology. 2020;158(8):2139–2149.
2. Vermeire S, et al. J Crohns Colitis. 2021;15(Suppl1):S021-S022.
3. Panaccione R, et al. LBA 64, ACG 2021, 22–27 October.
4. Colombel JF, et al. Effect of upadacitinib (UPA) treatment on extraintestinal manifestations (EIMs) in patients with moderate-to-severe Ulcerative Colitis (UC): Results from the UPA Phase 3 programme. OP33, ECCO 2022, 16–19 February.

Upadacitinib effector pathways unravelled

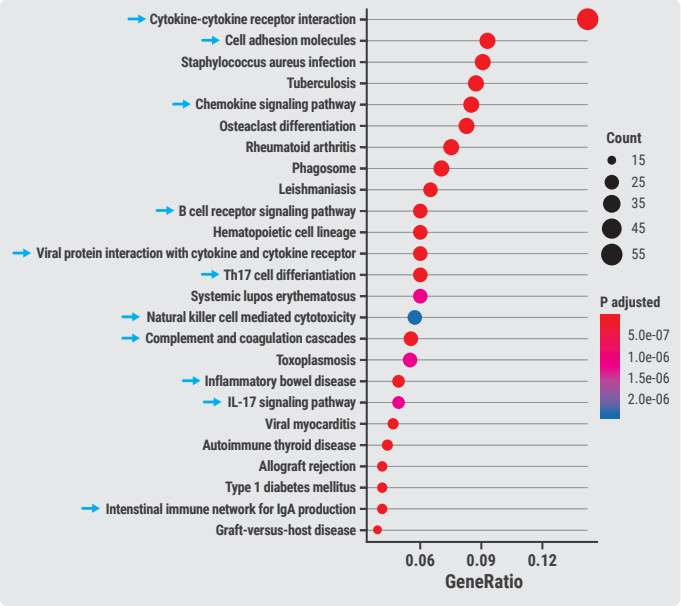
Upadacitinib therapy suppresses pathogenic inflammatory pathways and positively affects tissue-resident cells associated with gut barrier function and mucosal repair in participants with ulcerative colitis (UC), according to an analysis of the phase 2b U-ACHIEVE data. In addition, participants who achieved the stringent histo-endoscopic mucosal response (HEMR) endpoint displayed a unique transcriptional modulation of the gut microenvironment.

Dr Bram Verstockt (KU Leuven, Belgium) and colleagues aimed to investigate the effect of upadacitinib on the inflamed intestinal microenvironment in patients with UC and link molecular modulations of pathogenic pathways to upadacitinib efficacy outcomes [1]. For this purpose, data was analysed from the placebo, 15 mg, 30 mg, and 45 mg upadacitinib arms of the phase 2b U-ACHIEVE study (NCT02819635). Differential expression analysis, pathway enrichment, responder analysis, and gut cell deconvolution were performed.

Responders to upadacitinib showed significantly more differentially expressed genes (DEGs) than non-responders. The amount of DEGs increased for participants who responded to more stringent endpoints, such as endoscopic improvement or histologic improvement. Notably, responders displayed an increase in both downregulated and upregulated DEGs. Furthermore, upadacitinib was able to modulate many pathways that are key in UC pathogenesis, including chemokine signaling, B-cell receptor signaling, and Th17 cell differentiation. In addition, more general pathways were modulated, such as inflammatory bowel disease or chemotactic pathways (see Figure).

Next, cell deconvolution demonstrated significant downregulation of inflammatory cells after 8 weeks of upadacitinib treatment in responders, including CD4-effector T cells, T-regulatory cells, and plasma cells. Notably, the data showed that these effects were counterbalanced by an increase in enterocytes, secretory goblet cells, and myofibroblasts. This suggests that upadacitinib therapy is not only resulting in downregulation of inflammatory pathways but also actively contributes to gut barrier function and wound healing mechanisms in responders. Additional data on the downregulation of CD4 T cells indicates that Th17, Th2, Th9, and Th1 subsets of CD4 T cells may be involved. However, this result should be interpreted with caution and further studies are needed to confirm this.

Figure: KEGG pathway enrichment of downregulated genes from baseline to week 8 [1].



Finally, the more stringent the endpoint, the more genes were differentially modulated in responders. This was particularly the case for various histologic outcomes. Especially the HEMR, the most stringent endpoint, showed a large modulation of differentially expressed genes in responders.

"There seems to be a robust and unique transcriptional modulation of the gut microenvironment that is associated with this novel endpoint," according to Dr Verstockt.

1. Verstockt B, et al. Upadacitinib modulates inflammatory pathways in gut tissue in patients with Ulcerative Colitis: Transcriptomic profiling from the Phase 2b study, U-ACHIEVE. OP30, ECCO 2022, 16–19 February.

Deucravacitinib does not meet primary endpoint for ulcerative colitis

Deucravacitinib did not significantly improve response rates or clinical remission rates in participants with active ulcerative colitis (UC) compared with placebo. Pharmacodynamical data of the phase 2 LATTICE-UC

trial showed that the target tyrosine kinase 2 (TYK2) was hit but that the dose may have been insufficient to reduce inflammation in participants with UC. Another phase 2 trial has been initiated to investigate a higher dose of deucravacitinib.

Deucravacitinib is an oral, selective TYK2 inhibitor. The randomised, double-blind, placebo-controlled phase 2 LATTICE-UC trial (NCT03934216) was conducted to assess the safety and efficacy of this agent in patients with active UC. In total, 131 participants with moderately to severely active UC who failed at least 1 prior therapy were randomised 2:1 to 6 mg deucravacitinib twice daily (n=88), or placebo (n=43). The primary endpoint was clinical remission[a]. Prof. Silvio Danese (Vita-Salute San Raffaele University, Italy) presented the results [1].

At week 12, the primary endpoint was not met. Clinical remission was achieved by 14.8% of the participants in the deucravacitinib arm and by 16.3% of the participants in the placebo arm (P=0.59). In participants who had failed on 1 or more prior biologic therapies, proportion of participants achieving clinical remission was 16.1%.

Deucravacitinib was well tolerated in the LATTICE-UC trial and the safety profile was consistent to deucravacitinib's safety profiles in psoriasis trials. Adverse events (AEs) were reported in 70.1% and 47.6% of the participants in the experimental arm and placebo arm, respectively. Serious AEs were observed in 9.2% of the participants in the deucravacitinib arm and 4.8% of the participants in the placebo arm. Rash (11.5%), acne (9.2%), and UC (6.9%) were the most common AEs in participants treated with deucravacitinib.

Prof. Danese mentioned that pharmacological data showed that TYK2 engagement was observed without a subsequent effect on downstream inflammatory markers. According to Prof. Danese, this result suggests that the deucravacitinib dosing may have been too low to translate into clinical benefits for the participants. Therefore, another phase 2 trial (NCT04613518) is currently ongoing to investigate a higher dose of deucravacitinib in patients with UC.

a. *Clinical remission is defined as modified Mayo score with subscores of stool frequency ≤1 with ≥1-point decrease from baseline, rectal bleeding of 0, and endoscopic subscore ≤1 excluding friability*

1. Danese S, et al. Efficacy and safety of deucravacitinib, an oral, selective tyrosine kinase 2 inhibitor, in patients with moderately-to-severely active Ulcerative Colitis: 12-week results from the Phase 2 LATTICE-UC study. DOP42, ECCO 2022, 16–19 February.

Head-to-Head Comparisons

Anti-TNFs versus vedolizumab and ustekinumab in Crohn's disease

A post-hoc analysis of pivotal clinical trials showed that the TNF inhibitors adalimumab and infliximab generally outperformed vedolizumab and ustekinumab with regard to endoscopic healing of the ileum and colon in participants with Crohn's disease (CD). However, in biologic-naïve participants, TNFs and ustekinumab did not display significant differences for endoscopic healing of the colon.

Recent evidence has demonstrated that large ulcers of the ileum and rectum are less likely to heal with infliximab compared with other biologic therapies. In addition, no trials have been conducted to compare biologic therapies for ileal and colonic healing in patients with CD.

Dr Neeraj Narula (McMaster University, Canada) and colleagues performed a pooled analysis that included 344 participants with CD who were enrolled in clinical trials [1]. All participants had received continuous adalimumab, infliximab, ustekinumab, or vedolizumab. The primary endpoint was 1-year endoscopic healing, defined as a simple endoscopic score for Crohn's disease (SES-CD) of 0. Results were adjusted for potential confounders including disease duration, concomitant corticosteroid use, and prior anti-TNF failure.

In participants with ileal involvement, vedolizumab showed the lowest proportion of patients achieving one-year endoscopic healing (18.6%), whereas infliximab was associated with the highest proportion compared with vedolizumab (36.7%; P=0.038). In addition, adalimumab (30%; P=0.225) and ustekinumab (22.7%; P=0.694) demonstrated numerically

higher rates of segment endoscopic healing than vedolizumab but were not significant. Similar results were obtained in participants who displayed ileal ulcers >5 mm. Notably, there was no significant difference between biologic therapies for endoscopic healing in biologic-naïve participants with ileal involvement: adalimumab (37.5%) versus vedolizumab (21.9%; P=0.200); infliximab (36.7%) versus vedolizumab (P=0.130); ustekinumab (40.0%) versus vedolizumab (P=0.255).

Among participants with colonic disease, ustekinumab showed the lowest rate of colonic endoscopic healing (29.0%). Adalimumab (62.5%; P<0.001) and infliximab (52.4%; P=0.041) demonstrated significantly higher rates of colonic endoscopic healing compared with ustekinumab. Vedolizumab was associated with an endoscopic healing rate of 31.3% and did not differ from ustekinumab (P=0.987). In participants with colonic ulcers >5 mm, infliximab and adalimumab had the highest colonic endoscopic healing rates, whereas ustekinumab had the lowest endoscopic healing rate. These results were similar in biologic-naïve participants.

"Despite that these results were confirmed in multivariate analysis, our study cannot compete with a true head-to-head study," admitted Dr Narula. "Moreover, the rapidity of onset of the compared biologics may partially explain the results we have observed. Certain biologic treatments need to be continued for a longer time before endoscopic healing occurs. Nonetheless, TNF inhibitors were in general superior to vedolizumab and ustekinumab for reaching endoscopic healing of the ileum and colon in these participants."

1. Narula N, et al. Comparative Efficacy of Biologics for Endoscopic Healing of the Ileum and Colon in Crohn's Disease. OP10, ECCO 2022, 16–19 February.

Upadacitinib appears to be an efficacious therapy for moderately-to-severely ulcerative colitis

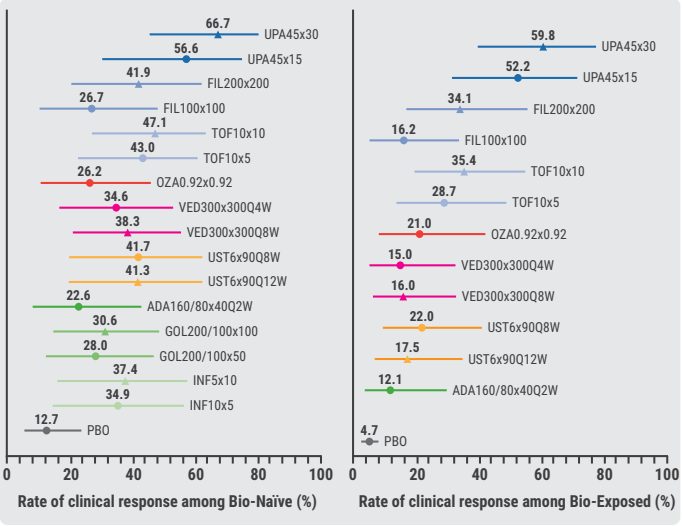
Upadacitinib 45 mg induction therapy followed by 30 mg maintenance therapy showed the highest efficacy in a Bayesian network meta-analysis, indirectly comparing therapies for patients with moderately to severely active ulcerative colitis (UC). In addition, the safety profile of upadacitinib was similar to the safety profiles of other advanced therapies for this population.

The comparative efficacy and safety of recently developed therapies for patients with UC has not been established. A Bayesian network meta-analysis was conducted by Prof. Remo Panaccione (University of Calgary, Canada) and colleagues to compare advanced induction and maintenance therapies for patients with moderately to severely active UC [1]. The study included all therapies with published phase 3 data (i.e. ustekinumab, filgotinib, tofacitinib, infliximab, vedolizumab, adalimumab, golimumab, upadacitinib, and ozanimod). All therapies were compared with placebo.

In biologic-naïve participants, upadacitinib 45 mg induction therapy displayed the largest difference in clinical response[a] rates compared with placebo (OR 6.9). Also, filgotinib 200 mg (OR 3.4), tofacitinib (OR 3.1), ustekinumab (OR 3.6), and infliximab 5 mg (OR 3.4) displayed high response rates. Endoscopic improvement[b] rates confirmed the superior efficacy of upadacitinib induction therapy (OR 6.9), and ozanimod demonstrated high efficacy rates compared with placebo as well (OR 3.6). In biologic-exposed participants, the JAK inhibitors as a class performed well in inducing clinical remission, especially upadacitinib (OR 9.8) and tofacitinib (OR 5.2). In addition, ustekinumab was efficacious in this population, with an OR of 5.9 in inducing clinical remission compared with placebo.

Treat-through analysis in biologic-naïve participants after induction and maintenance therapy showed the highest clinical response rates in participants treated with upadacitinib 45 mg induction and 30 mg maintenance therapy (66.7%), followed by upadacitinib 45 mg induction and 15 mg maintenance therapy (56.6%). This result was confirmed in biologic-experienced participants, with corresponding clinical response rates of 59.8% and 52.2% (see Figure).

Figure: Clinical response rate treat-through analysis in bio-naïve and bio-exposed participants [1]



The safety analysis showed that upadacitinib induction and maintenance therapies were not associated with a higher rate of adverse events than other advanced therapies. The rate of serious adverse events in participants treated with upadacitinib induction therapy and upadacitinib 15 mg or 30 mg maintenance therapy were 3.6%, 4.4%, and 3.8%, respectively.

Prof. Panaccione concluded that upadacitinib induction and maintenance therapies appear to be more efficacious than other advanced therapies regarding clinical response, clinical remission, and endoscopic response rates in both biologic-naïve and biologic-experienced patients with moderately-to-severely UC.

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a. Clinical response is defined as a decrease from baseline in full Mayo Score ≥3 points and ≥30% with decrease in rectal bleeding score of ≥1 or absolute rectal bleeding score ≤1

b. Endoscopic improvement is defined as an endoscopic score ≤1.

1. Panaccione R, et al. Efficacy and safety of advanced induction and maintenance therapies in patients with moderately to severely active Ulcerative Colitis: An indirect treatment comparison using Bayesian network meta-analysis. OP34, ECCO 2022, 16–19 February.

Subcutaneous infliximab versus subcutaneous vedolizumab in IBD

Subcutaneous infliximab therapy outperformed subcutaneous vedolizumab therapy in participants with Crohn's disease (CD), according to a comparative analysis. In participants with ulcerative colitis (UC), the 2 therapies appeared to be equally efficacious. The safety profiles of subcutaneous infliximab and vedolizumab therapies were comparable over 1 year of follow-up in both CD and UC.

Prof. Laurent Peyrin-Biroulet (Nancy University Hospital, France) compared the efficacy of subcutaneous infliximab and subcutaneous vedolizumab induction and maintenance therapies in participants with CD and UC, using data from 7 randomised-controlled trials [1]. The infliximab subcutaneous trial (NCT02883452) was compared with trials on vedolizumab including GEMINI II, GEMINI III, and VISIBLE 2 for CD and GEMINI I, VISIBLE 1, and VARSITY for UC.

In participants with CD, subcutaneous infliximab induction therapy was superior to subcutaneous vedolizumab induction therapy (all non-overlapping 95% CI intervals) with regard to Crohn's Disease Activity Index (CDAI)-70 response (79% [95% CI 0.66-0.88] vs 45% [0.32-0.60]), CDAI-100 response (62% [0.49-0.74] vs 36% [0.29-0.44]), clinical remission[a] rate (49% [0.36-0.62] vs 17% [0.12-0.24]), and discontinuations due to lack of efficacy (5% [0.01-0.28] vs 32% [0.26-0.39]). Moreover, subcutaneous infliximab maintenance therapy displayed higher CDA-100 response (64% [0.51-0.76] vs 47% [0.33-0.62]) and clinical remission rates (57% [0.43-0.69] vs 42% [0.31-0.54]) than subcutaneous vedolizumab maintenance therapy in participants with CD. In participants with UC, the therapies appeared to be equally efficacious. The safety profiles of the 2 therapies were comparable.

Prof. Peyrin-Biroulet added that not all participants in the vedolizumab trials were biologic-naïve. "Since we know that previous exposure to a TNF inhibitor may reduce the efficacy of vedolizumab, a subgroup analysis needs to be performed to compare the efficacy of subcutaneous infliximab and vedolizumab therapies in biologic-naïve and biologic-experienced patients."

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a. Clinical remission is defined as an absolute CDAI score <150 points.

1. Peyrin-Biroulet L, et al. A comparative efficacy and safety analysis of subcutaneous infliximab and vedolizumab in patients with Crohn's Disease and Ulcerative Colitis. DOP73, ECCO 2022, 16–19 February.

Vedolizumab outperforms anti-TNF in biologic-naïve ulcerative colitis

After 1 year of maintenance therapy, vedolizumab demonstrated higher clinical response rates than anti-TNF therapy in biologic-naive participants with ulcerative colitis (UC). Also, the treatment persistence was higher for vedolizumab therapy than for anti-TNF therapy, results from the real-world evidence, head-to-head VEDO-IBD study showed. Therefore, vedolizumab may be suggested as first-line biologic therapy in patients with UC.

The VEDO-IBD study (NCT03375424) was conducted to compare vedolizumab and anti-TNF therapies head-to-head in biologic-naïve and biologic-experienced patients with UC (n=1,200). The real-world evidence induction study included 314 biologic-naïve participants who were treated according to the physician's preference and reported comparable response rates among vedolizumab receivers (51.8%) and anti-TNF receivers (54.2%). The 1-year follow-up analysis conducted by Dr Bernd Bokemeyer (University Hospital Schleswig-Holstein, Germany) and colleagues included 274 biologic-naïve participants with UC [1]. Clinical response[a] rate and clinical remission[b] rates were measured.

At week 52, treatment persistence was higher among vedolizumab receivers (83.5%) than among anti-TNF

receivers (59.5%; P<0.001). In addition, the modified intention-to-treat analysis showed a higher response rate for participants treated with vedolizumab compared with participants treated with anti-TNFs (61.7% vs 40.3%; OR 2.39; 95% CI 1.39–4.10). In addition, the clinical remission rates (38.2% vs 26.0%) and corticosteroid-free remission rates (36.5% vs 24.0%) were not significant in participants treated with vedolizumab. Furthermore, both treatment groups displayed a significant improvement in quality of life from baseline but no difference in improvement of quality of life was observed between treatment groups.

Dr Bokemeyer concluded that the long-term results of this study show that vedolizumab is associated with a higher treatment persistence and a slightly higher effectiveness than anti-TNFs, suggesting that vedolizumab may be the preferred biologic therapy in biologic-naïve patients with UC.

a. Clinical response is defined as a reduction of partial Mayo score from baseline to 1-year by >3 points or a reduction of at least 30% compared with baseline or reaching remission at 1-year.

b. Clinical remission is defined as a partial Mayo score ≤1 plus a bleeding subscore of 0 and no systemic use of steroids or budesonide at 1-year.

1. Plachta-Danielzik S, et al. Maintenance phase propensity score adjusted effectiveness and persistence at week-52 in biologic-naïve Ulcerative Colitis patients treated with vedolizumab or anti-TNF (VEDO IBD-study). OP17, ECCO 2022, 16–19 February.

Short-Term and Long-Term Treatment Results

Ozanimod treatment shows maintained response in ulcerative colitis

Ozanimod demonstrated long-term durability of efficacy in participants with active ulcerative colitis (UC). Moreover, results from the open-label, extension study of the phase 3 True North trial did not display new safety issues associated with the long-term use of ozanimod.

Ozanimod is an S1P receptor modulator, approved for the treatment of patients with moderately to severely active UC based on the 52-week results of the True North trial (NCT02435992) [1]. An open-label extension study was initiated to assess the long-term efficacy of ozanimod [2]. In total, 823 participants entered the open-label extension study of the True North trial, of whom 64%, 34%, and 14% completed the week 46, week 94, and week 142 time points, respectively. Lack of efficacy (21%) and withdrawal by subject (13%) were the main reasons for treatment discontinuations. Prof. Silvio Danese (Vita-Salute San Raffaele University, Italy) presented the results.

Observed-case analysis showed maintained clinical remission[a] rates at week 46 (45%, n=203/452), week 94 (51%, n=109/213), and week 142 (45%, n=39/87). Among participants who displayed a clinical response[b] upon open-label extension entry, clinical remission rates were sustained at week 46 (70%, n=107/152) and week 94 (69%, n=42/61). Furthermore, clinical responses, endoscopic improvement rates, and corticosteroid-free remission rates demonstrated similar patterns of maintained efficacy of ozanimod in the study population.

No new safety issues were reported with the long-term use of ozanimod. The most commonly reported treatment-emergent adverse events (TEAEs) were lymphopoenia (10.3%; n=119), anaemia (7.9%; n=91), and nasopharyngitis (7.5%; n=87). Serious TEAEs were observed in 14% (n=162) of the participants. UC worsening (3.9%; n=45) was the only serious TEAE that occurred in more than 1% of the participants.

In conclusion, the current interim analysis of the True North open-label extension study demonstrated the long-term durability of efficacy and safety of ozanimod therapy in participants with moderately-to-severely active UC.

a. Clinical remission is defined as a rectal-bleeding subscore of 0; a stool-frequency subscore of ≤1 or less, with a decrease of at least 1 point from baseline; and an endoscopy subscore of 1 or less (all on scales from 0 [none] to 3 [most severe]).

b. Clinical response is defined as a reduction in the total Mayo score of ≥3 points and ≥30% from baseline or in the three-component Mayo score of ≥2 points and ≥35% from baseline, as well as a reduction in the rectal-bleeding subscore of ≥1 point or an absolute rectal-bleeding subscore of ≤1 point.

1. Sandborn WJ, et al. NEJM. 2021;385:1280–1291.
2. Danese S, et al. Long-term use of ozanimod in patients with moderately to severely active Ulcerative Colitis. DOP44, ECCO 2022, 16¬–19 February.

Stopping infliximab but not antimetabolites leads to more relapses in Crohn's disease

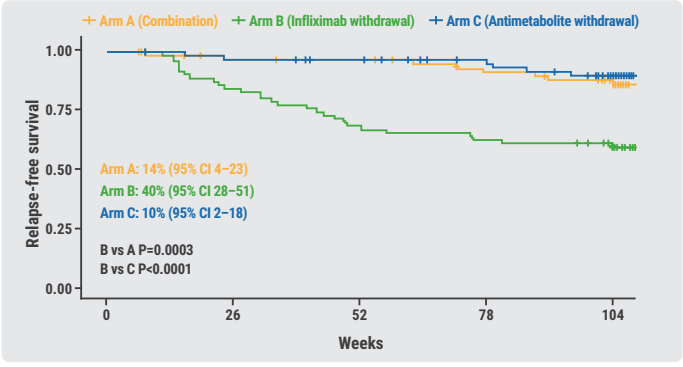
In patients with Crohn's disease (CD) who achieved sustained remission on infliximab plus antimetabolite therapy, infliximab discontinuation was associated with an increased risk of relapse in the phase 4 SPARE trial. In contrast, antimetabolite discontinuation did not lead to significantly higher relapse rates compared

with continuation of the combination treatment. Since physicians often contemplate de-escalation of infliximab plus antimetabolite therapy, these results may inform the decision-making process of treatment de-escalation in patients with CD.

"Infliximab in combination with antimetabolite therapy is a standard option for patients with CD," explained Prof. Edouard Louis (University Hospital Liège, Belgium) [1]. "Clinicians may contemplate de-escalation of this therapy if sustained remission is achieved." The current, prospective, randomised-controlled, phase 4 SPARE trial (NCT02177071) aimed to assess the relapse rates in patients who continued or withdrew from this combination therapy. Participants with CD (n=211) treated with infliximab and antimetabolites who achieved sustained steroid-free remission (>6 months) were randomised to infliximab withdrawal (n=71), antimetabolite withdrawal (n=69), or therapy continuation (n=71). If relapse occurred, participants were retreated with the agent they withdrew from. The primary endpoints were relapse rate and time spent in remission over 2 years.

Participants who withdrew from infliximab showed significantly higher 2-year relapse rates than participants who continued the combination therapy (40% vs 14%; log-rank P=0.0003) or than participants who discontinued antimetabolite treatment (40% vs 10%; log-rank P<0.0001; see Figure). Notably, 22 out of 23 participants in the infliximab discontinuation arm who relapsed and were subsequently retreated with infliximab achieved remission rapidly. This trend is reflected in the mean time spent in remission, which was only 6 days shorter in the infliximab arm compared with the continuation arm and 14 days shorter compared with the antimetabolite discontinuation arm. Although these differences are small, the pre-specified, non-inferiority criterion for stopping infliximab was not met.

Figure: Relapse rate over time [1]



1. Louis E, et al. Withdrawal of infliximab or anti-metabolite therapy in Crohn's Disease patients in sustained remission on combination therapy: A randomized unblinded controlled trial (SPARE). OP01, ECCO 2022, 16–19 February.

Vedolizumab first approved therapy for chronic pouchitis

Vedolizumab showed clinical, endoscopic, and histologic benefits over placebo in participants with chronic pouchitis after ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC). The safety profile of vedolizumab was consistent with previous data published on this agent. The phase 4 EARNEST trial is the first and largest randomised-controlled trial to demonstrate significant benefits of a biologic therapy in patients with chronic pouchitis.

Prof. Simon Travis (University of Oxford, UK) explained that although antibiotics are the standard treatment for acute pouchitis, therapies for chronic antibiotic-refractory pouchitis are lacking [1]. Therefore, the double-blind, placebo-controlled EARNEST trial (NCT02790138) randomised participants with chronic pouchitis after proctocolectomy with IPAA for UC (n=102) 1:1 to vedolizumab (300 mg, intravenous, administered at day 1 and weeks 2, 6, 14, 22, and 30) or placebo. Additionally, all participants received 500 mg twice daily ciprofloxacin for the first 4 weeks. Remission at week 14, defined by a modified Pouchitis Disease Activity Index (mPDAI) score <5 and a ≥2-point reduction from baseline, was the primary endpoint of this study.

Vedolizumab outperformed placebo with respect to the primary endpoint (mPDAI remisson 31.4% vs 9.80%; P=0.013). In addition, mPDAI response rates favoured vedolizumab over placebo after 14 weeks (62.7% vs 33.3%; P=0.003) and 34 weeks (51.0% vs 29.4%; P=0.026). Sustained mPDAI remission rates were higher in the vedolizumab arm than in the placebo arm (27.5% vs 5.90%). Furthermore, larger histologic and endoscopic improvements were seen in participants who were treated with vedolizumab. "These improvements in pouchitis disease activity among participants treated with vedolizumab were reflected in improvements in health-related quality of life," added Prof. Travis. At week 34, IBDQ remission rates (score ≥ 170) were observed in 43% of the patients on vedolizumab and in 19.6% of the patients on placebo (95% CI 4.9-40.7).

The safety analysis did not show new safety issues of vedolizumab. Treatment-related adverse events occurred in 21.6% and 23.5% of the participants in the placebo group and the vedolizumab group, respectively. In total, 5 adverse events-related treatment discontinuations were reported in the placebo arm compared with 1 in the vedolizumab arm.

"On 31 January 2022, vedolizumab was approved by the EMA for the treatment of adult patients with moderately to severely

active chronic pouchitis who underwent proctocolectomy and IPAA for UC and displayed an inadequate response to antibiotics," concluded Prof. Travis.

1. Travis S, et al. Vedolizumab intravenous is effective across multiple treatment targets in chronic pouchitis: Results of the randomised, double-blind, placebo-controlled EARNEST trial. OP04, ECCO 2022, 16–19 February.

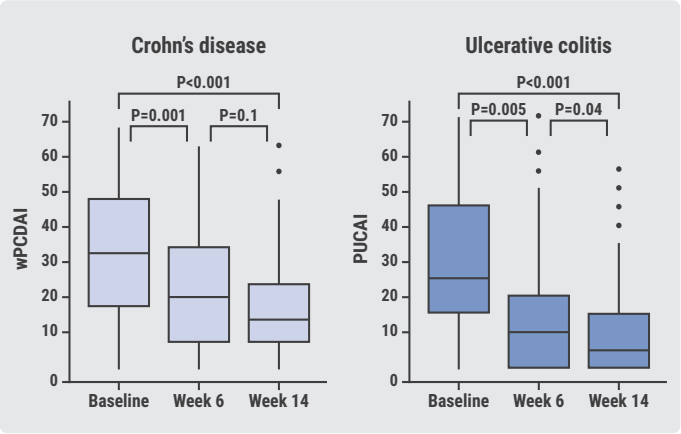
VEDOKIDS: Vedolizumab seems effective in paediatric IBD

Vedolizumab induction therapy was effective in paediatric participants with inflammatory bowel disease (IBD). The prospective, multicentre VEDOKIDS study also showed that disease severity at baseline might predict the response to vedolizumab in this population. Since data on the use of vedolizumab in children with IBD are limited, this study helps to understand the applicability of this agent in paediatric patients with IBD.

The VEDOKIDS study (NCT02862132), a prospective cohort study, included 142 children (0–18 years) with Crohn's disease (CD; n=65) or ulcerative colitis (UC; n=77), of whom approximately 68% had failed on previous anti-TNF treatment [1]. The participants were exposed to intravenous vedolizumab 177 mg/m2 Body Surface Area (BSA) up to a maximum of 300 mg at weeks 0, 2, 6 and then every 8 weeks. Clinical remission, defined as steroid-free and exclusive enteral nutrition (EEN)-free remission, was the main clinical outcome of the study. The results at week 14 were presented by Dr Dan Turner (Juliet Keidan Institute of Paediatric Gastroenterology and Nutrition, Israel).

At week 14, 40% of the participants with CD achieved clinical remission and 21% reached steroid-free remission with normal erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP). For participants with UC, the corresponding figures were 51% and 36%. Moreover, significant treatment effects were already observed at week 6 (see Figure). Clinical remission proportions in participants receiving vedolizumab as first-line or second-line therapy were not significantly different, suggesting a comparable efficacy of vedolizumab in biologic-naïve participants and participants who failed on a biologic therapy. Notably, disease activity at baseline, measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI), was predictive of clinical remission at week 14 (AUC 0.66; 95% CI 0.54–0.79). Moreover, Mucosal Inflammation Non-invasive (MINI) index (AUC 0.79; 95% CI 0.64–0.94) and weighted Pediatric Crohn's Disease Activity Index (wPCDAI) scores (AUC 0.70; 95% CI 0.57–0.84) were predictive of

Figure: Rapid improvement in clinical activity [1]



clinical remission. Dr Turner added that children >30 kg could be dosed as adults (300 mg), whereas children <30 kg may be dosed with 200 mg or 10 mg/kg.

In total, 114 adverse events were reported. Of these adverse events, 32 were possibly related to vedolizumab therapy. Fortunately, all of those events were mild or moderate. Only 2 adverse event-related treatment discontinuations were reported: 1 case of leukocytoclastic vasculitis and 1 case of dyspnoea.

1. Shavit Z, et al. Outcome of induction therapy with vedolizumab in children: Results from the prospective, multi-centre VEDOKIDS study. OP05, ECCO 2022, 16–19 February.

Primary endpoint of 5-hydroxytryptophan for fatigue in IBD not met

5-hydroxytryptophan was not superior to placebo in reducing fatigue among participants with quiescent inflammatory bowel disease (IBD) in the phase 2 Trp-IBD trial. However, a reduction in fatigue was reported in both treatment groups, suggesting that supporting therapies and attention for fatigue may have improved symptoms in these patients.

Fatigue is common among patients with IBD, with 72% of the patients with active disease and 47% of the patients in remission reporting this symptom, explained Dr Marie Truyens (Ghent University Hospital, Belgium) [1]. Since tryptophan has been associated with fatigue in IBD, a multicentre, double-blind, cross-over, randomised-controlled trial (NCT03574948) was conducted to assess the efficacy of 5-hydroxytryptophan supplementation in fatigued patients with inactive IBD. The participants were randomised to 5-hydroxytryptophan first, 100 mg twice daily (n=82), or placebo first (n=84) for 8 weeks. Subsequently, the participants

switched treatment groups. The primary endpoint was the proportion of participants with ≥20% reduction on the Visual Analogue Scale for Fatigue (fatigue-VAS).

After 16 weeks, approximately 35% of the 166 participants in either treatment group showed a ≥20% reduction on the fatigue-VAS. Since no significant difference was reported between the treatment groups (P=0.830), the primary endpoint was not met. In addition, similar reductions in depression, anxiety, and stress were reported for participants receiving placebo and participants receiving 5-hydroxytryptophan. Next, increases in 5-hydroxytryptophan and serotonin levels were observed, but these were not related to a reduction in fatigue.

Dr Truyens argued that the reduction in fatigue that was observed among placebo receivers may be associated with the extra attention that was given to this symptom. "Fatigue is often overlooked in patients with IBD. Additional clinical support and increased patient awareness may have resulted in a reduction in fatigue in this study population."

1. Truyens M, et al. A randomized placebo controlled clinical trial with 5-hydroxytryptophan in patients with quiescent Inflammatory Bowel Disease and fatigue (Trp-IBD). OP28, ECCO 2022, 16–19 February.

Specific Therapeutic Strategies

Positive outcomes with therapeutic drug monitoring during infliximab maintenance therapy

Proactive therapeutic drug monitoring (TDM) outperformed standard therapy in maintaining disease control in participants with immune-mediated inflammatory diseases (IMID) who were on infliximab maintenance therapy in the 52-week NOR-DRUM B trial. The results indicate that TDM should be used as a general strategy for patients on infliximab maintenance therapy.

"It is not yet established whether proactive TDM improves clinical outcomes in patients who are on infliximab maintenance therapy," said Dr Kristin Jørgensen (Akershus University Hospital, Norway) [1,2]. Therefore, the NOR-DRUM A and B randomised-controlled clinical trials (NCT03074656) assessed proactive TDM during the induction and maintenance phase of infliximab therapy in participants with IMID [2]. The NOR-DRUM A trial demonstrated a non significant difference between TDM and standard therapy during infliximab induction therapy with regard to clinical remission at week 30. The multicentre NOR-DRUM B trial randomised 450 participants with IMID 1:1 to TDM or standard therapy to assess the efficacy of TDM on disease control during infliximab maintenance therapy. TDM was performed proactively before each infusion. If the drug level was outside of the therapeutic window (3.0–8.0 mg/L) a dose increase or reduction was considered.

A significantly higher proportion of participants displayed disease control in the TDM arm (74%) compared with the standard therapy arm (56%; P<0.001). For concomitant immunosuppressive therapy there were comparable baseline characteristics: 54.2% in TDM arm, 57.3% in standard therapy arm. All disease categories numerically favoured TDM over standard therapy regarding disease control, with a significant adjusted difference for the 2 largest diagnosis groups, ulcerative colitis (22.3%; 95% CI 1.6-43.1) and spondyloarthritis (20.9%; 95% CI 6.0-35.8). In addition, the adjusted difference in disease control between TDM and standard therapy was 17.4% (95% CI -5.5-40.3) in participants with Crohn's disease. The mean dose and serum-infliximab levels were comparable for both groups. However, more participants in the standard therapy arm displayed drug levels below the therapeutic window.

The safety analysis demonstrated comparable safety profiles for the 2 study groups. Any adverse events (AEs) occurred in 60% and 63% of the participants in the TDM arm and the standard therapy arm, respectively. Serious AEs were reported in 7% of the participants receiving TDM and in 8% of the participants receiving standard therapy. Dr Jørgensen added that infusion-related reactions were more frequently observed in the standard therapy arm.

"The effect was mostly driven by the drug serum levels of the participants," argued Dr Jørgensen. "Controlling these

levels was therefore the most important part of TDM. The development of anti-drug antibodies was less relevant and only observed in a few participants. These results support the use of proactive TDM in patients with IMID on infliximab maintenance therapy. However, future studies should investigate the cost-effectiveness of this approach and compare reactive TDM with proactive TDM."

1. Syversen SW, et al. JAMA. 2021;325(17):1744–1754.
2. Jørgensen KK, et al. Proactive Therapeutic Drug Monitoring is superior to standard treatment during maintenance therapy with infliximab; results from a 52-week multicentre randomised trial of 450 patients; the NOR-DRUM B study. OP09, ECCO 2022, 16–19 February.

Segmental colectomy beneficial over total colectomy in Chrohn's disease

Segmental colectomy (SC) was not associated with an increased risk of surgical recurrence compared with total colectomy (TC) in participants with Crohn's disease (CD). In addition, SC did reduce the risk of a temporary or permanent stoma. The large-scale, international, multicentre SCOTCH study adds high-quality data to the understanding of colectomy in CD.

According to existing guidelines, SC is appropriate in patients with a single involved colonic segment. However, data on SC and TC in patients with CD and multiple involved colonic segments is limited and of low quality, according to Dr Gianluca Pellino (University of Campania Luigi Vanvitelli, Italy) [1]. Therefore, the current SCOTCH trial aimed to compare the surgical recurrence rates, perioperative complications, and stoma formation rates of SC and TC in participants with primary, colonic CD (n=687). SC was defined as the resection of 1–3 segments, whereas TC involved the resection of >3 segments.

The surgical recurrence rate was significantly higher in participants who underwent TC compared with those who underwent SC (P=0.006). This result did not change with the number of segments involved (P=0.2). Furthermore, participants who underwent TC had an increased risk of a temporal stoma (31.6% vs 21.4%; P=0.0007) or a permanent stoma (39.3% vs 8%; P<0.0001). In addition, re-admissions occurred more frequently in participants who underwent TC (6% vs 2.1%; P=0.02).

Postoperative treatment with biologics reduced the risk of recurrence (25% vs 51%; P<0.001) in patients with 1–3 segments involved. Perioperative complications were numerically more frequently reported in the TC arm than in the SC arm but did not differ significantly (P=0.07). The rate of major complications was similar for the 2 groups (10.2% and 9.7%; P=0.9). Interestingly, not receiving biologic therapy was a significant predictor of recurrence (HR 5.4; P<0.0001). In addition, perianal CD (HR 1.9) and CD diagnosis before 18 years of age (HR 2.7) were predictive of recurrence.

Dr Pellino argued that these findings may be practice changing. "SC may be discussed in patients with limited colonic disease, younger patients, and those who do not display inflammatory extensive colitis, but rather have penetrating or structuring disease. The results clearly show the importance of biologic therapies in the setting of colectomy. To conclude, future studies should thoroughly investigate the application of SC in ulcerative colitis as well."

1. Pellino G, et al. Segmental vs Total Colectomy for Crohn's disease of the colon in the biologic era. Results from the SCOTCH international, multicentric study. OP12, ECCO 2022, 16¬–19 February.

Modified 2-stage ileal pouch-anal anastomosis versus 3-stage alternative

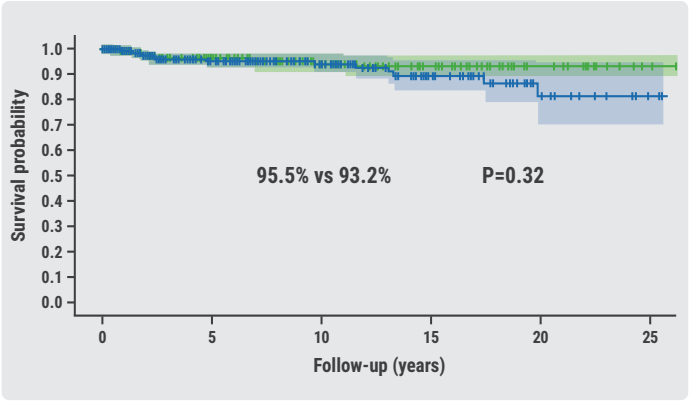
Similar long-term outcomes were reported for participants who received modified 2-stage or 3-stage ileal pouch-anal anastomosis (IPAA). However, the modified 2-stage approach should only be performed by experienced surgeons at high-volume centres and in a select group of patients.

Long-term outcomes of modified 2-stage IPAA have not yet been evaluated, according to Dr Stefan Holubar (Cleveland Clinic Foundation, OH, USA) [1]. The modified 2-stage approach is defined as completion proctectomy without loop ileostomy, whereas the 3-stage approach includes completion proctectomy with loop ileostomy. For this study, 223 participants from the Adult Pouch Registry who underwent modified 2-stage IPAA between 1983 and 2019 were matched with 223 participants who underwent 3-stage IPAA. The primary outcome was pouch survival, defined by permanent diversion, pouch excision, and conversion to a Kock pouch.

Long-term pouch survival outcomes were similar between participants who underwent modified 2-stage or 3-stage IPAA (95.5% vs 93.2%; P=0.32; see Figure). However, 3-stage participants had a shorter postoperative length of hospital stay than modified 2-stage participants (5 vs 8 days; P<0.001). Also, a numerically but not significantly higher complication rate was reported in the modified 2-stage arm (17.0% vs 12.1%; P=0.09). Functional outcomes were mostly similar for the investigated approaches. The number of stools per 24 hours was 7 in both groups. Similarly, the

proportion of participants requiring seepage protection at night did not significantly differ between the 3-stage and modified 2-stage arm (29.7% vs 24.6%; P=0.31). Participant satisfaction levels were comparable.

Figure: Kaplan-Meier curve for pouch survival (matched pairs) [1]



Dr Holubar said that modified 2-stage IPAA may be an alternative for patients with limited options. However, he emphasised that the modified 2-stage approach should only be performed by experienced surgeons in high-volume centres. Moreover, the eligible patient profile for modified 2-stage IPAA is highly selective. "Patients should display minimal pouch tension, 3 or lower on a scale from 1 to 10, have perfect betadine leak tests prior to anastomosis, and perfect endoscopic leak tests after anastomosis. Also, the physiology of the patient needs to fit the procedure."

1. Holubar S, et al. Modified 2-stage vs. 3-stage ileal pouch-anal anastomosis result in equivalent long-term functional outcomes and pouch survival: A matched-pair analysis. OP13, ECCO 2022, 16–19 February.

Similar results for different corticosteroid tapering protocols in UC

Different prednisolone tapering algorithms did not affect the short-term or long-term effectiveness of infliximab in participants with ulcerative colitis (UC). However, subgroup analysis showed participants with acute severe UC may benefit from standard tapering compared with fast tapering or direct discontinuation of corticosteroids.

Corticosteroids are administered in more than 50% of the patients with UC in the first 5 years after diagnosis [1]. In patients with acute severe UC, corticosteroids are often administered in combination with TNF inhibitors. However, data is limited on the role of corticosteroid tapering in this population. The current, retrospective, single-centre study investigated the impact of prednisolone tapering algorithms on the short-term and long-term effectiveness of infliximab in patients with UC [2]. Participants were categorised according to the following tapering protocol: standard (≤5 mg/week; n=42), fast (>5 mg/week; n=25), direct discontinuation (n=10), or no prednisolone administered (n=71). Corticosteroid-free clinical remission was the clinical endpoint of the study (defined as a partial Mayo score ≤1). Ms Pernille Ovesen (Herlev University Hospital, Denmark) presented the short-term (week 14) and long-term (week 52) results.

At week 14, no significant differences in corticosteroid-free clinical remission rates were reported for participants who underwent standard corticosteroid tapering (57.1%), fast tapering (36.0%), direct discontinuation (40.0%) or those who did not receive prednisolone (40.8%). However, the C-reactive protein levels <5 mg/L significantly favoured the standard tapering arm (100%) over the fast-tapering arm (77.8%; P=0.03) and the direct discontinuation arm (60.0%; P=0.03). The results after week 52 did not display a significant effect of tapering protocols on clinical remission or response rates in the overall study population.

A subgroup analysis, including 33 participants with acute severe UC, did show a significant benefit of the standard tapering protocol over fast tapering with regard to corticosteroid-free clinical remission rates (66.7% vs 23.5%; P<0.05) at week 14.

"The data indicates that a longer corticosteroid exposure might improve infliximab responses in patients with a higher disease burden," concluded Ms Ovesen.

1. Burisch J, et al. J Crohns Colitis. 2019;13(2):198¬208.
2. Ovesen PD, et al. The influence of different prednisolone tapering algorithms on the effectiveness of infliximab in patients with ulcerative colitis – a real-world cohort study. OP06, ECCO 2022, 16–19 February.

Miscellaneous Topics

Lessons from the COVID-19 pandemic for IBD management

Prof. Siew Ng (Chinese University of Hong Kong, Hong Kong) discussed the current evidence on inflammatory bowel disease (IBD) and COVID-19. The risk of COVID-19 in patients with IBD, the impact of IBD medication on COVID-19 severity, and guidance on COVID-19 vaccines in patients with IBD were the main topics.

Risk of COVID-19

"In general, patients with IBD do not have an increased risk of contracting COVID-19," said Prof. Ng. The incidence of COVID-19 among patients with IBD is relatively low (0.3%) compared with the general population (0.2–4.0%) [1,2]. In addition, it has been shown that the use of anti-TNFs or thiopurines does not lead to an increased risk of contracting COVID-19 [3]. Regarding COVID-19 outcomes, it has been demonstrated that patients with IBD who are older, male, have comorbidities, or higher disease activity, are more likely to experience worse outcomes, such as hospitalisation, ventilation, or death [4].

IBD medication and COVID-19

"The use of corticosteroids has consistently been associated with an increased risk of worse COVID-19 disease outcomes in patients with IBD," continued Prof Ng. "In contrast, biologic agents, immunomodulators, and mesalamines were not related to worse COVID-19 outcomes." Therefore, IBD medications do not need to be discontinued or reduced during the current pandemic, except for corticosteroids, which should be reduced whenever possible.

Vaccines and IBD

"The current evidence suggests that COVID-19 vaccines are not associated with an increase in IBD flares or other adverse events. Also, in patients with IBD, full vaccination, but not partial vaccination, resulted in a 69% reduced hazard of SARS-CoV-2 infection compared with unvaccinated patients with IBD. Therefore, patients with IBD should be vaccinated at the earliest opportunity to do so. In addition, patients who are treated with corticosteroids, anti-TNF monotherapy or combination therapy, or tofacitinib may have a compromised vaccine response. This could result in an increased risk for breakthrough SARS-CoV-2 infections. In general, a third dose is recommended in patients with IBD, especially since the arrival of the highly contagious Omicron variant [5]. Even a fourth vaccine dose might be warranted in certain patients. However, more studies need to be conducted to establish the value of a fourth COVID vaccination in patients with IBD."

1. Ng S, et al. Lessons from the COVID pandemic for IBD management. SCI40, ECCO 2022, 16–19 February.
2. Aziz M, et al. Inflam Bowel Dis. 2020;26(10):e132–e133.
3. Khan N, et al. Gastroenterology. 2020;159(4):1592–1594.
4. Singh S, et al. Gastroenterology. 2020;159(4):1575–1578.
5. Alexander J, et al. COVID-19 vaccine-induced antibody responses are impaired in Inflammatory Bowel Disease patients treated with infliximab, ustekinumab or tofacitinib, but not thiopurines or vedolizumab. OP21, ECCO 2022, 16–19 February.

AI model distinguishes between histologic activity and remission in ulcerative colitis

A novel artificial intelligence (AI) model was able to distinguish between histological remission and disease activity in biopsies of participants with ulcerative colitis (UC). The model can improve the histological evaluation of patients in clinical practice; an evaluation that is key in distinguishing mild activity from remission.

Although there are over 30 histological score systems, the use of these tools in clinical practice is limited, according to Dr Tommaso Parigi (Humanitas University, Italy). The largest obstacles for daily practice are the high interobserver variability and the complexity of the available score systems. The current study aimed to develop a simple and reliable histological score that is implementable in an AI system. The next objective was to develop an AI model to distinguish histological activity from remission. In total, 614 biopsies from the PICaSSO study were used to develop the score system [1,2].

The novel PICaSSO Histologic Remission Index (PHRI) measures the presence of neutrophils in epithelium and lamina propria. PHRI displayed a correlation with endoscopic assessment ranging between 0.69–0.78, depending on the endoscopic score system that was used for comparison. Moreover, it shows excellent inter-reader agreement (ICC 0.84). Subsequently, the authors created an AI model based on the PHRI to detect neutrophils and discriminate between disease activity and remission. The data of the AI model was compared with the gold standard of an annotation by a human pathologist.

Neutrophil detection via AI had a sensitivity of 0.72, a specificity of 0.84, a positive predictive value of 0.75, a negative predictive value of 0.83, and an accuracy of 0.80. Furthermore, the AI model showed a high specificity (0.94) and positive predictive value (0.90) for the detection of disease activity. The sensitivity, negative predictive value, and accuracy for detecting disease activity were 0.62, 0.73, and 0.79, respectively.

Dr Parigi added that this AI model might eventually replace the pathologist for histologic assessments. However, the sensitivity needs to be improved, and the AI should be further trained to predict other histologic scores.

1. Villanacci V, et al. A new simplified histology artificial intelligence system for accurate assessment of remission in Ulcerative Colitis. OP15, ECCO 2022, 16–19 February.
2. Iacucci M, et al. Gastroenterology. 2021;160(5):1558–1569.

Multi-Omic and dietary analysis of Crohn's disease identifies pathogenetic factors

Dietary differences between participants with Crohn's disease (CD) at diagnosis and healthy controls were observed in an analysis of the Israelian Sheba cohort. The consumption of vitamin D, olive oil, and vegetables was reduced in participants with CD, whereas their sugar, starch, and nitrite intake was increased in this group. Moreover, integration between dietary and transcriptomics, metabolomics, and the microbiome revealed novel pathogenetic factors.

Dr Yael Haberman (Sheba Medical Center, Israel) and colleagues aimed to decipher dietary, environmental, and host factors that drive the increasing incidence of CD [1]. For this purpose, they collected dietary, transcriptomic, metabolomic, environmental, and microbial data from 25 participants with CD at CD diagnosis and 33 healthy controls.

The dietary analysis showed that vitamin D, olive oil, and vegetable intake was significantly lowerd in participants with CD compared with healthy controls. In contrast, sugar, starch, and nitrite consumption was higher. The environmental questionnaire did not reveal significant differences between the study groups.

Microbial data (feacal and mucosal biopsies) demonstrated significant differences between participants with CD and healthy controls, with increased levels of *Enterobacteriaceae Ruminococcus gnavus* in participants with CD and decreased levels of *Ruminococceae Lachnospiraceae*. In addition, it was shown that biopsy samples compared with stool samples were enriched with pathogenic bacteria like *Veillonella*, *Fusobacterium*, *Neisseria*, and *Ruminococcus gnavus*.

Furthermore, metabolite serum analysis revealed that oxalate, GABA, and serotonin serum levels were significantly higher in participants with CD, whereas decanoic and octanoic acid serum levels were lower compared with healthy controls. Dr Haberman added that participants with CD consume fewer vegetables than controls, have lower levels of *Oxalobacter formigenes* in their stool but display higher serum levels of oxalate than controls, suggesting that participants with CD may have less oxalate degradation in the gut.

Transcriptomics of the ileum demonstrated a reduction in epithelial genes and pathways, such as GUCA2B, SLC10A2, MT1A, and GSTA1. Also, an increase of DUOX2, CXCL9, CSF2, and DEFB4A was observed, which are innate epithelial pro-inflammatory genes and immune signatures linked to the extracellular matrix.

Subsequently, host transcriptomics were linked to dietary factors via co-expression models. According to Dr Haberman, these models may help to re-direct disease recommendations in individual patients with Crohn's disease.

1. Haberman Y, et al. Dietary and Multi-Omic characterization of new onset treatment naive Crohn Disease identifies factors that may contribute to disease pathogenesis. OP31, ECCO 2022, 16–19 February.

Novel classification system for perianal fistulising Crohn's disease

A new patient-oriented classification system for perianal fistulising Crohn's disease (PFCD) has been developed by expert consensus. The new classification system includes treatment suggestions per class and patient-specific recommendations for clinical trial suitability.

"PFCD has a prevalence of 14 to 43% among patients with CD and significantly reduces the quality of life of these patients," said Dr Jeroen Geldof (University Hospital Ghent, Belgium) [1]. "In addition, the current classification systems for PFCD lack a clear connection with the clinical practice. By means of a modified nominal group expert consensus process, 4 groups of patients with PFCD were identified." The 'treat to patient' goal was the basis of each category. Dr Philip Tozer (St Mark's Hospital and Academic Institute, UK) outlined the different classes of the new classification system [2].

Class 1 – **Patients with minimal disease:** these patients have minimal symptoms or anorectal disease burden over time, and require minimal intervention.

Class 2 – **Patients with chronic symptomatic fistulae:**

Class 2a – Patients with symptomatic fistulae that are suitable for combined medical/surgical closure. The goal is fistula closure.

Class 2b – Patients with chronic symptoms related to fistulae that are currently unsuitable for surgical repair. The goal is symptom control.

Class 2c-i – Patients with early and rapidly progressive disease. These patients may require early intervention with defunctioning ostomy or proctectomy.

Class 2c-ii – Patients with gradually debilitating disease who are unsuitable for surgical repair and experience severely reduced quality of life. Defunctioning ostomy is required to improve the quality of life. The goal is symptom control.

Class 3 – **Patients with exhausted perineum or adverse features:** these patients have severely symptomatic disease despite defunctioning ostomy, with irreversible perineal destruction or adverse features such as concomitant anorectal stricture, refractory proctitis, or complex fistulae. These patients require proctectomy.

Class 4 – **Patients with perineal symptoms after proctectomy:**

Class 4a – Patients with symptomatic sinuses or wounds that are suitable for medical/surgical repair. The goal is sinus closure.

Class 4b – Patients with chronic symptoms related to sinuses or wounds that are unsuitable for surgical repair. The goal is symptom control.

The clinical trial suitability of the patient is related to the goal of the class that the patient is sorted into. For example, a patient in class 2a is suitable for trials that investigate interventions in which the primary outcome measure is fistulae closure, whereas a patient in class 2b could participate in a clinical trial that has symptom control or quality of life gains as the primary outcome measure.

The authors aim to develop specific treatment algorithms per class and validate the classification system retrospectively and prospectively. Eventually, the study group also intends to evaluate the long-term impact of the classification system on patient satisfaction and clinical outcomes.

1. Tozer P, et al. Classifying perianal fistulising Crohn's Disease: An expert-consensus to guide decision-making in daily practice and clinical trials. OP19, ECCO 2022, 16–19 February.
2. Geldof J, et al. Lancet Gastroenterol Hepatol. 2022;S2468-1253(22)00007–3.

Vaccination tool associated with improved vaccination coverage in IBD

The integration of a vaccination tool in the electronic medical record of patients with immune-mediated inflammatory diseases (IMID) was significantly associated with an improved vaccination rate. This integrated tool may help to overcome the suboptimal vaccination rates in patients with IMID that were measured in 2018 and during the COVID-19 pandemic.

An optimal vaccination rate among patients with IMID is important since these patients are at a higher risk for infectious diseases, according to Ms Liselotte Fierens (KU Leuven, Belgium) [1]. However, many patients do not achieve the guideline-recommended vaccination coverage. In a population of patients with IMID, only 27.4% had a full vaccination coverage in 2018. Ms Fierens and colleagues integrated a vaccination module in the electronic health record of the university hospital of Leuven to document and monitor the vaccination status of patients. Followed were 1,448 patients with IMID, of whom 798 were patients with inflammatory bowel diseases (IBD). The current vaccination status of these patients was compared with their vaccination status before the introduction of the vaccination tool in 2018.

In the whole study population, the vaccination coverage increased from 27.4% in 2018 to 51.9% in 2021 (P<0.001). In patients with IBD, the vaccination coverage increased from 42.2% to 60.4% (P<0.001). In addition, the proportion of specific vaccinations increased between 2018 and 2021 in patients with IBD, including influenza (75.9% vs 86.3%; P<0.001), pneumococci (72.9% vs 88.7%; P<0.001), hepatitis B (66.0% vs 80.2%; P<0.001), and tetanus (79.9% vs 85.7%; P=0.041). Ms Fierens concluded that this study demonstrated that the integration of a vaccination tool in the electronic health record of patients with IBD and other IMIDs improved the vaccination coverage in this at-risk population.

1. Fierens L, et al. Implementation of a vaccination tool in the electronic patient health record significantly increased vaccination coverage. P115, ECCO 2022, 16–19 February.

Comparable safety profiles of biological therapies in elderly patients with IBD

A systematic review comparing the safety profiles of biological therapies in elderly patients with inflammatory bowel disease (IBD) did not reveal significant differences in the rate of adverse events (AEs) between the different treatments. However, infusion/injection reactions occurred more often in patients treated with anti-TNFs. The authors

concluded that larger studies are needed to establish sequencing recommendations of biological therapies in this population.

Dr Gustavo Drügg Hahn (McGill University Health Center, Canada) and colleagues conducted a systematic review and meta-analysis to study the safety profiles of biological therapies in elderly patients with IBD [1]. In total, 17 studies assessing the safety profiles of anti-TNFs, vedolizumab, and ustekinumab in participants with IBD aged 60 years or older were included in the systematic review.

No significant difference was detected in the rate of AEs for participants treated with anti-TNFs, vedolizumab, or ustekinumab (mean rate 11.3/100 patient-years; P=0.11). In addition, the infection rate associated with the use of these therapies was comparable (mean rate 9.5/100 patient-years; P=0.56). Participants on anti-TNFs displayed significantly more infusion/injection-related AEs than participants treated with vedolizumab or ustekinumab (P=0.02). In addition, participants treated with vedolizumab/ustekinumab demonstrated higher malignancy rates (P=0.01), though this might be caused by a selection bias of the physician to be more likely to start vedolizumab or ustekinumab in patients with a high risk for malignancy based on the beneficial safety profiles of the new biologicals reported in the clinical trials. The systematic review included 2 studies that directly compared the safety and efficacy of anti-TNFs and vedolizumab, showing similar efficacy and safety of these agents in elderly participants with IBD [2,3].

1. Drügg Hahn G, et al. Safety of Biological Therapies in Elderly IDB: a Systematic Review and Meta-analysis. P318, ECCO 2022, 16–19 February.
2. Adar T, et al. Aliment Pharmacol Ther. 2019;49(7):873–879.
3. Pable BS, et al. Dig Dis Sci. 2021 Jul 15. Doi: 10.1007/s10620-021-07129-5.

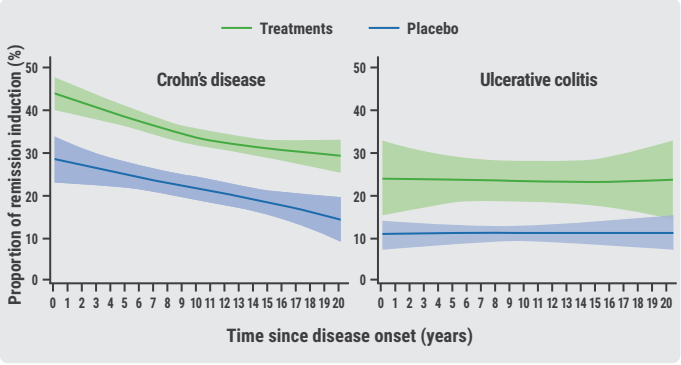
Early biologic therapy induces larger effect than delayed treatment in Crohn's disease

The benefit of biologic therapy versus placebo was similar for participants with short-term or long-term inflammatory bowel disease (IBD) in a recent systematic review. However, in participants with Crohn's disease (CD), the absolute effects of both placebo and biologic therapies were larger in participants with short-term disease, implying that early treatment is important in these patients.

Prof. Shomron Ben-Horin (Tel-Aviv University, Israel) and colleagues conducted a systematic review to assess the treatment effect of biologic therapies in patients with short duration (≤18 months) and long duration (>18 months) IBD [1,2]. The study included 25 trials, investigating infliximab, adalimumab, certolizumab, golimumab, natalizumab, or vedolizumab with a total of 9,395 patients with IBD. The primary endpoint was the proportional benefit of biologic treatments compared with placebo with regard to the induction of remission[a].

The relative benefit of active treatment versus placebo was similar for participants with short-term CD (risk ratio 1.47; 95% CI 1.01–2.15) or long-term CD (risk ratio 1.43; 95% CI 1.19–1.72). In addition, no significant interaction effect was reported for treatment effect and disease duration (P=0.585). Similarly, for participants with ulcerative colitis (UC), the active-to-placebo treatment relative benefit was not significantly different between participants with short-term disease (risk ratio 1.82; 95% CI 1.12–2.97) or long-term disease (risk ratio 2.21; 95% CI 1.79–2.72). Notably, the absolute effects of both biologics and placebo were higher in participants with short-term CD compared with participants with long-term CD. In the UC population, this pattern was not observed (see Figure).

Figure: Absolute effects of biologics and placebo in IBD [1,2]



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Prof. Ben-Horin argued that the greater absolute benefits of both active therapy and placebo may be due to the greater plasticity of early CD. Another explanation may be that patients with early disease show a higher placebo response because they are more amenable to suggestions. However, further studies are warranted to investigate the explanations behind the observed larger absolute treatment effect in patients with early CD.

a. *Induction of remissions for CD was defined as a Crohn's Disease Activity Index <150 and for UC as a total Mayo score ≤2 with no individual subscore >1.*

1. Ben-Horin S, et al. Efficacy of biologic drugs in short-duration versus long-duration Inflammatory Bowel Disease: A systematic review and an individual-patient data meta-analysis of randomized controlled trials. DOP62, ECCO 2022, 16–19 February.
2. Ben-Horin S, et al. Gastroenterology. 2022;162(2):482–494.

RESTORE-UC: No better outcomes with FMT superdonors than with autologous stools

The use of superdonor stools for faecal microbiota transplantation (FMT) did not outperform autologous stools in initiating remission in participants with active ulcerative colitis (UC). The current RESTORE-UC trial also presented an FMT anaerobic preparation and administration protocol to improve the international standardisation of this therapy.

Dr Clara Caenepeel (KU Leuven, Belgium) explained that FMT, a novel therapy for active ulcerative colitis, has shown variable success rates in randomised-controlled trials. The results of these trials indicate that the efficacy of FMT may be influenced by donor and procedural characteristics [1]. Therefore, the RESTORE-UC trial (NCT03110289) aimed to assess whether donor preselection on the microbiota level, using a strict anaerobic approach, and repeated FMT administration (4 FMTs) may enhance FMT outcomes in patients with active UC [2]. Superdonors were selected, excluding those with *Bacteroides2* enterotype, or those with high proportions of *Fusobacterium*, *Escherichia coli* and *Veillonella*. Donors with the lowest microbial loads were excluded. The enrolled participants were randomised 1:1 to autologous FMT or superdonor FMT. The primary endpoint was steroid-free clinical remission(defined as total Mayo score ≤2, with all subscores ≤1) and steroid-free endoscopic remission (defined as Mayo endoscopy subscore ≤1) after 8 weeks. The results of the 66% futility analysis were presented (n=70).

The primary endpoint was not met. Superdonor stools were not associated with higher rates of steroid-free clinical and endoscopic remission than autologous stools (10.0% vs 13.9%; P=0.72). The secondary endpoints displayed similar results. FMT was in general safe and well tolerated, according to Dr Caenepeel. In total, 76.9% and 23.1% of the participants experienced adverse events (AEs) in the autologous arm and the superdonor arm, respectively. Two serious AEs were reported, 1 case of dysuria and 1 case of worsening colitis. Both of these events occurred in the autologous arm.

Dr Caenepeel argued that the negative results of this trial need to be investigated thoroughly. “Perhaps the endpoint we chose for this study was too bold. However, it could be that our perspective on donor selection is still too simplistic. Therefore, I believe that future studies should assess factors other than microbiota, such as immunity and genetics.”

1. Sun D, et al. Medicine. 2016;95(23):e3765.
2. Caenepeel C, et al. Standardized faecal microbiota transplantation with microbiome-guided donor selection in active UC patients: A randomized, placebo-controlled intervention study. OP03, ECCO 2022, 16–19 February.