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PEER-REVIEWED CONFERENCE REPORT

VIVID-1: Mirikizumab meets expectations in CD

Mirikizumab met its primary endpoints in the phase 3 VIVID-1 trial for patients with moderate-to-severe Crohn's disease, regardless whether a prior biologic therapy had failed them or not.

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PROFILE benefits patients with early CD

The PROFILE study's top-down treatment strategy improved outcomes compared with an accelerated step-down treatment strategy in patients with newly diagnosed Crohn's disease, without increasing infection risk.

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Promising JAK inhibitors in CD

The phase 2 PIZZICATO trial showed that both ritlecitinib and brepocitinib were associated with improved efficacy outcomes compared with placebo in patients with moderate-to-severe Crohn's disease.

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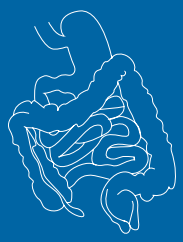

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MEDICAL PUBLISHERS

Head Office
Medicom Medische Uitgeverij B.V.
Laarderhoogtweg 25
1101 EB Amsterdam
The Netherlands

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

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

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Letter from the Editor

Dear Esteemed Readers,

Welcome to the latest edition of our publication, where we continue our commitment to delivering insightful and cutting-edge updates from the field of gastroenterology. As we delve into the diverse array of topics in this issue, it's evident that the landscape of gastroenterological research and practice is constantly evolving, driven by innovative discoveries and groundbreaking advancements.

In this edition, we are delighted to present a comprehensive report covering the European Crohn's and Colitis Organisation (ECCO) Congress 2024, which took place in Stockholm. This prestigious event brought together leading experts and practitioners from around the world to share their knowledge and insights into the latest developments in the field.

As we explore the content of this edition, we shine a spotlight on the rising prominence of IL-23 inhibitors, exploring their increasing utilisation and efficacy in managing various gastrointestinal disorders. From the encouraging outcomes of mirikizumab in Crohn's disease as demonstrated in the VIVID-1 trial to the long-term benefits of risankizumab in ulcerative colitis showcased in the COMMAND study, our coverage provides valuable insights into the expanding therapeutic options available to patients and clinicians alike.

Furthermore, our exploration extends to inspiring drug trials and treatment strategies, including the promising potential of novel agents like VTX002 in ulcerative colitis and the benefits of a top-down treatment approach for patients with early Crohn's disease (PROFILE). We also delve into the evolving landscape of JAK inhibitors, examining their efficacy in Crohn's disease, microscopic colitis and their role as a rescue option for acute severe ulcerative colitis.

As we navigate through the latest advancements in endoscopy, screening, and risk factors, we address critical questions surrounding the use of AI-assisted endoscopy in predicting relapse in ulcerative colitis and the importance of genetic testing, such as NUDT15 testing, in optimising treatment outcomes for patients with Asian ancestry.

Last but not least, our focus extends to surgical solutions, where we explore the nuances of surgical approaches in Crohn's disease, including the debate between extended mesenterectomy and mesenteric-sparing surgery (SPICY trial) and KONO-S and side-to side anastomosis, as well as the outcomes of darvadstrocel in complex peri-anal fistula in the ADMIRE-CD-II trial.

We are confident that this edition will serve as a valuable resource for practitioners, researchers, and all those dedicated to advancing the field of gastroenterology. We extend our gratitude to the contributors, researchers, and clinicians whose dedication and expertise continue to drive progress in our understanding and treatment of gastrointestinal disorders. We hope you find this edition both informative and enlightening.

Best regards,
Marjolijn Duijvestein

Biography

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:
Marjolijn Duijvestein 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.

IL-23 Inhibitors on the Rise

VIVID-1: Mirikizumab meets expectations in Crohn's disease

Mirikizumab met its primary endpoints in the phase 3 VIVID-1 trial, testing this agent among patients with moderate-to-severe Crohn's disease (CD). The response rates were comparable between participants, regardless whether a prior biologic therapy had failed them or not.

Mirikizumab is a novel IL-23p19 inhibitor that has been approved for the treatment of patients with moderate-to-severe ulcerative colitis and has shown promising efficacy data among patients with CD [1].

To further assess the value of mirikizumab in CD, the multicentre, double-blind, placebo- and active-controlled, phase 3 VIVID-1 study (NCT03926130) randomised 1,150 adult patients with moderate-to-severe CD 6:3:2 to mirikizumab, ustekinumab, or a placebo [2]. In the mirikizumab arm, participants received 900 mg i.v. every 4 weeks during the induction phase, and 300 mg s.c. every 4 weeks during the maintenance phase. Furthermore, in the placebo arm, non-responders were re-randomised to mirikizumab or placebo after 12 weeks of therapy.

Prof. Marc Ferrante (University Hospitals Leuven, Belgium) presented the first results of the co-primary endpoints, being:

- clinical response (defined as ≥30% decrease in stool frequency and/or abdominal pain, and neither score worse than baseline) at week 12 plus endoscopic response (defined as ≥50% reduction from baseline in Simple Endoscopic Score for Crohn's Disease [SES-CD] Total Score) at week 52, and
- clinical response (defined as ≥30% decrease in stool frequency and/or abdominal pain, and neither score worse than baseline) at week 12 plus clinical remission (defined as Crohn's Disease Activity Index [CDAI] Total Score <150) at week 52.

The first co-primary endpoint was met by 38.0% of the participants in the mirikizumab arm and by 9.0% of the participants in the placebo arm (Δ28.7; 95% CI 20.6–36.8; P<0.0001), with consistent results among bio-naïve and bio-experienced participants. Next, 45.4% of the mirikizumab receivers and 19.6% of the placebo receivers achieved the second co-primary endpoint (Δ25.8; 95% CI 15.9–35.6; P<0.0001). These results were sustained in the more stringent secondary efficacy endpoints, such as a combined clinical response at week 12 and endoscopic remission at week 52 (23.5% vs 4.0%; 95% CI 13.1–25.7; P<0.0001). Finally, the safety profile of mirikizumab was consistent with the known favourable safety profile of this agent among patients with ulcerative colitis.

"Mirikizumab demonstrated significant and clinically meaningful improvements in primary and secondary efficacy endpoints compared with placebo in this population of patients with CD, with an acceptable safety profile," decided Prof. Ferrante.

1. Sands BE, et al. Gastroenterology. 2022;162:495-508.
2. Ferrante M, et al. Primary efficacy and safety of mirikizumab in moderate to severe Crohn's disease: results of the treat-through VIVID 1 study. OP05, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

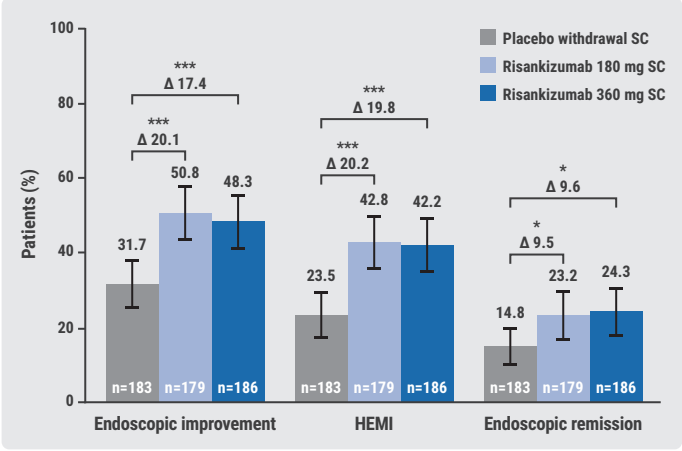
COMMAND: Long-term efficacy benefits of risankizumab in ulcerative colitis

In patients with moderately to severely active ulcerative colitis (UC) who responded to risankizumab induction therapy, risankizumab maintenance therapy outperformed placebo withdrawal treatment regarding various clinical, endoscopic, and patient-reported outcomes.

INSPIRE (NCT03398148), a previous phase 3 induction trial, demonstrated the superiority of the IL-23 inhibitor risankizumab (1,200 mg i.v.) over placebo in terms of clinical and endoscopic endpoints in patients with UC [1]. The current phase 3 COMMAND trial (NCT03398135) enrolled 588 patients with UC who responded to the 12-week induction regimen of INSPIRE [2]. These participants were randomised 1:1:1 to risankizumab, either 180 mg or 360 mg s.c., every 8 weeks, or a placebo. Clinical remission (defined as modified Mayo score [MMS] stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore =0, and endoscopic subscore ≤1) at week 52 was the primary endpoint, and Prof. Stefan Schreiber (University Hospital Schleswig-Holstein, Germany) presented the findings.

At week 52, 40.2% and 37.6% of the participants in the 180 mg and 360 mg groups achieved clinical remission, compared with 25.1% of the participants on placebo, significantly favouring the experimental arms over the control arm. This difference appeared to be more pronounced among adequate responders to prior advanced therapy (50.9% in the 180 mg group, 61.7% in the 360 mg group, vs 31.1% on placebo) but was still present among participants who did show an inadequate response to a previous advanced therapy (36.6% in the 180 mg group, 29.5% in the 360 mg group, vs 23.2% on placebo). Endoscopic, histologic, patient-reported, and more stringent clinical endpoints all favoured risankizumab over placebo in this population (see Figure). Lastly, the drug was well tolerated and the safety profile was consistent with previously published data.

Figure: Histologic and endoscopic endpoints at week 52 in the COMMAND trial [2]



HEMI, Histological-endoscopic mucosal improvement; *P<0.05; ***P<0.001

"Risankizumab maintenance therapy was superior to placebo withdrawal treatment in patients with UC who responded to risankizumab induction therapy, without substantial toxicity," concluded Prof. Schreiber.

1. Louis et al. Abstract OP021, UEG Journal. 2023;11(S8).
2. Schreiber S, et al. Risankizumab maintenance therapy in patients with moderately to severely active ulcerative colitis: efficacy and safety in the randomized phase 3 COMMAND study. OP06, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

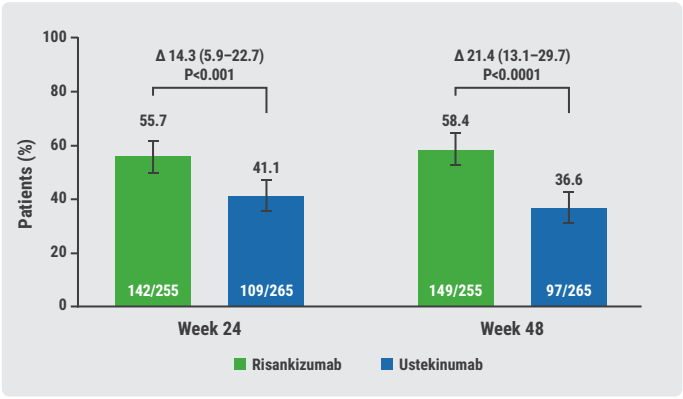
SEQUENCE: Risankizumab versus ustekinumab across endpoints

Risankizumab outperformed ustekinumab regarding symptom improvement, clinical response and remission rates, and patient-reported outcomes, across all timepoints, in patients with moderate-to-severe Crohn's disease (CD) for whom at least 1 prior TNF inhibitor had failed. This was shown in an updated analysis of the phase 3b SEQUENCE trial.

"STRIDE-II recommendations suggest that symptom relief should be an early treatment goal for patients with moderate-to-severe CD," stated Prof. Marla Dubinsky (Mount Sinai Hospital, NY, USA) [1,2]. The SEQUENCE trial (NCT04524611) compared risankizumab and ustekinumab in patients with moderate-to-severe CD who had been treated with 1 or more anti-TNF agents (n=520). The participants were randomised in a 1:1 fashion and a previous presentation had demonstrated that the primary endpoints –week 24 clinical remission and week 48 endoscopic remission– were met [3]. Prof. Dubinsky presented updated and additional results for various clinical endpoints [2].

"Crohn's Disease Activity Index (CDAI) clinical response (defined as reduction of CDAI ≥100 points from baseline) significantly improved in participants receiving risankizumab compared with those receiving ustekinumab at week 8 (60.7% vs 51.3%), week 24 (69.8% vs 54.3%), and week 48 (67.4% vs 46.8%)," expressed Prof. Dubinsky. Moreover, in the updated data set, CDAI clinical remission (defined as CDAI ≤150) rates continued to significantly favour risankizumab over ustekinumab at week 24 (59.6% vs 42.6%) and week 48 (60.8% vs 40.8%). Similar results were observed for stool frequency/abdominal pain score clinical remission at week 24 and week 48 (see Figure).

Figure: SF/APS clinical remission in the SEQUENCE trial [2]



SF/APS clinical remission defined as average stool frequency ≤2.8 and abdominal pain score ≤1, and neither worse than baseline.

"Greater symptom improvements and higher clinical response and clinical remission rates were seen in patients

on risankizumab than in patients on ustekinumab in this analysis that used the full dataset of the SEQUENCE trial," Prof. Dubinsky concluded.

1. Turner D, et al. Gastroenterology. 2021;160:1570-1583.
2. Dubinsky MC, et al. Risankizumab versus Ustekinumab for the achievement of clinical outcomes and symptom improvements in patients with moderate to severe Crohn's disease: results from the phase 3b SEQUENCE trial. OP36, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
3. Peyrin-Biroulet L, et al. Abstract LB01, UEG Journal. 2023;11(S8).

QUASAR: Guselkumab improves QoL for patients with ulcerative colitis

In the phase 3 QUASAR trial, guselkumab induction therapy delivered clinically meaningful improvements across all measured domains of health-related quality-of-life (QoL) compared with placebo in patients with moderately to severely active ulcerative colitis (UC).

The phase 3 QUASAR induction study (NCT04033445) assessed the efficacy and safety of the IL-23p19 inhibitor guselkumab in patients with moderately to severely active UC who had displayed intolerance or an inadequate response to a prior conventional therapy, biologic, or JAK inhibitor. The participants (n=701) were randomised 3:2 to guselkumab i.v. every 4 weeks, or a placebo. Prof. Julian Panés (Hospital Clinic de Barcelona, Spain) shared findings of the health-related QoL assessment, as measured by the patient-reported outcomes measurement information system (PROMIS)-29 [1].

At week 12, significantly higher proportions of participants in the guselkumab arm achieved clinically meaningful improvements (i.e. ≥5 point improvement) in symptom scores and function scores. The effect was observed across all domains of measured symptoms: anxiety (44.9% vs 25.4%), depression (39.0% vs 21.8%), fatigue (51.5% vs 30.0%), pain interference (44.2% vs 28.2%), and sleep disturbance (38.5% vs 20.4%), as well as across the 2 measured function domains: physical function (30.9% vs 19.3%) and social participation (50.4% vs 31.1%). Finally, pain scores, as measured by a numeric rating scale, were reduced with an average 1.69 points in the guselkumab arm and an average 0.95 points in the placebo arm.

"Patients with UC treated with guselkumab induction therapy in the QUASAR trial experienced broad and clinically meaningful improvements in health-related QoL, compared with patients who received placebo," concluded Prof. Panés.

1. Panés J, et al. Guselkumab improves health-related quality of life as measured by PROMIS-29 in patients with moderately to severely active ulcerative colitis: phase 3 QUASAR induction study. DOP49, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

Fatigue, urgency, and QoL improvements on mirikizumab in Crohn's disease

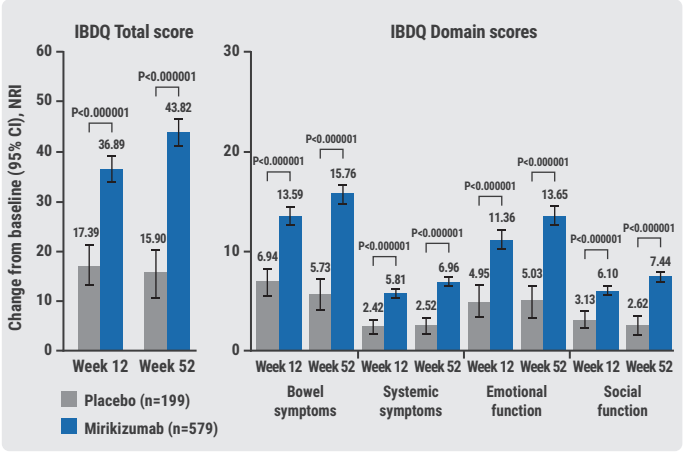
In the phase 3 VIVID-1 trial, mirikizumab improved fatigue, bowel urgency, and health-related quality-of-life (QoL) after 12 and 52 weeks, compared with placebo, in patients with moderately to severely active Crohn's disease (CD).

Prof. Simon Travis (University of Oxford, UK) shared patient-reported outcomes of patients with CD who received mirikizumab (n=579) or a placebo (n=199) in the phase 3 VIVID-1 study (NCT03926130) [1]. Fatigue was measured with the FACIT-fatigue instrument, bowel urgency was assessed with a numeric rating scale, and the Inflammatory Bowel Disease Questionnaire (IBDQ) was used to evaluate health-related QoL.

After 12 weeks of therapy, participants in the mirikizumab arm had an average of 5.86 points improvement in fatigue compared with an average of 2.64 points in participants on placebo (P<0.0001). At week 52, the corresponding figures were 7.47 and 3.08 (P<0.0001). "Already after 12 weeks, patients in the mirikizumab arm achieved the 5-point improvement that is considered a clinically meaningful difference," emphasised Prof. Travis.

Furthermore, bowel urgency was significantly improved among participants receiving mirikizumab compared with those receiving a placebo at week 12 (-2.44 vs -1.58; P<0.0001) and week 52 (-3.24 vs -1.23; P<0.0001). Finally, the IBDQ scores showed that health-related QoL had also improved in the experimental arm compared with the placebo arm at week 12 (+36.9 vs + 17.4; P<0.000001) and week 52 (+43.8 vs +15.9; P<0.000001). "These improvements were seen

Figure: IBDQ total and domain scores of mirikizumab versus placebo at week 12 and week 52 [1]



CI, confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; NRI, non-responder imputation.

across domain scores, such as bowel symptoms, systemic symptoms, emotional function, and social function," added Prof. Travis (see Figure on the previous page).

In conclusion, in the VIVID-1 trial, mirikizumab was superior to placebo in terms of improving fatigue, bowel urgency, and health-related QoL in patients with CD.

1. Travis S, et al. Mirikizumab improves fatigue bowel urgency, and quality of life in patients with moderately to severely active Crohn's disease: results from a phase 3 clinical trial. OP12, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

Inspiring Drug Trials and Treatment Strategies

Novel agent VTX002 holds promise in ulcerative colitis

The investigational, oral, selective, sphingosine-1-phosphate-1 (S1P1) receptor modulator VTX002 was associated with increased clinical, endoscopic, and histologic remission rates compared with placebo in patients with moderately to severely active ulcerative colitis (UC) in a phase 2 study. Moreover, the agent was well tolerated in this study population.

"Various S1P receptor modulators have been approved for the treatment of multiple sclerosis and/or UC, with ozanimod and etrasimod being available agents in UC," outlined Prof. Bruce Sands (Icahn School of Medicine at Mount Sinai, NY, USA) [1]. VTX002 is a novel S1P1 receptor modulator, with a different receptor selectivity than ozanimod and etrasimod.

In a multicentre, randomised, double-blind phase 2 trial (NCT05156125), Prof. Sands and colleagues tested VTX002 in patients with moderately to severely active UC. The participants (n=213) were randomised 1:1:1 to 60 mg VTX002 once daily, 30 mg VTX002 once daily, or a placebo. The primary endpoint was clinical remission (defined as modified Mayo score [MMS] stool frequency subscore ≤1, rectal bleeding subscore =0, and endoscopic subscore ≤1) at week 13.

In the 60 mg and 30 mg VTX002 arms, 27.9% and 23.9% of the participants achieved clinical remission by week 13, respectively; in the placebo arm, 11.4% achieved this endpoint. These findings significantly favoured the experimental arms over the placebo arm (P=0.018; P=0.041). Notably, the effect appeared to be present regardless of experience with advanced therapies.

Secondary efficacy endpoints, such as endoscopic improvement (36.8%; 32.4%; 15.7%), histologic remission (19.1%; 28.2%; 7.1%), and symptomatic remission (42.6%; 40.8%; 25.7%) all favoured the experimental arms over the placebo arm.

"The novel agent was generally well tolerated," stated Prof. Sands. The rate of adverse events (AEs) was somewhat higher in the experimental arms than in the placebo arm (47% vs 34.3%), but the rate of serious AEs was low with 2.7% and 4.3% in the 60 mg arm and 30 mg arm, respectively. "Finally, there were no cases of bradycardia, atrioventricular block, serious infections, macular oedema, or death," Prof. Sands noted.

In conclusion, VTX002 was associated with improved health outcomes compared with placebo and had an acceptable safety profile in a population of patients with moderately to severely active UC.

1. Sands BE, et al. Efficacy and safety of the oral selective sphingosine-1-phosphate-1 receptor modulator VTX002 in moderately to severely active ulcerative colitis: results from a randomised, double-blind, placebo-controlled, phase 2 trial. OP03, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

PROFILE: Top-down treatment strategy benefits patients with early Crohn's disease

A top-down treatment strategy resulted in improved outcomes compared with an accelerated step-down treatment strategy in patients with newly diagnosed Crohn's disease (CD), without increasing the risk of serious infections.

"There has been debate on whether a top-down or accelerated step-up treatment strategy should be utilised for the management of patients with previously untreated CD," said Dr Nuru Noor (Cambridge University Hospitals, UK) [1]. "Two prior prospective observational studies had validated a prognostic biomarker to identify patients at high risk of recurrent flares" [2,3]. The PROFILE trial (ISRCTN11808228) built on these observational studies and aimed to answer 2 questions [4]. First, can a prognostic biomarker guide management and improve outcomes for newly diagnosed patients with CD? Second, what is the optimal treatment strategy for these patients?

The research team used a blood-based biomarker to allocate the included participants (n=386) into a low-risk group (IBD-low) and a high-risk group (IBD-high) [1,2]. All participants started with a steroid taper for 2 weeks [1]. Subsequently, they were randomised 1:1 to a top-down strategy, in which participants started on infliximab and an immunomodulator, or an accelerated step-up strategy, in which participants started with a complete steroid wean and received an immunomodulator if a flare was observed, followed by infliximab in case of a second flare, and followed with a steroid taper if the patient had yet another flare. The primary endpoint was sustained steroid-free and surgery-free remission from the induction of steroids until week 48.

The median time from diagnosis to enrolment was 12 days. The primary endpoint was achieved by 79% of the participants in the top-down arm and by 15% of those in the step-up arm (Δ64%; 95% CI 57–72; P<0.0001). Next, Dr Noor showed that the biomarker did not demonstrate utility for stratifying to either treatment arm.

"Both adverse events and serious adverse events were lower with top-down therapy compared with accelerated step-up therapy. Looking at serious adverse events, we did not see any increase in serious infections in the top-down group (n=3) compared with the accelerated step-up group (n=8)," added Dr Noor. "Finally, we noticed that the need for urgent abdominal surgery was higher in the accelerated step-up arm than in the top-down arm" (post-hoc OR 0.095; 95% CI 0.0001–0.51).

Dr Noor highlighted that "the inclusion criteria for PROFILE were pragmatic and included patients with symptoms, raised inflammatory markers, and endoscopic evidence of disease activity. A definition which encompasses most patients presenting with a new diagnosis of active CD."

"These results indicate that a top-down treatment strategy should be utilised in the majority of patients with newly diagnosed active CD," concluded Dr Noor.

1. Noor N, et al. PROFILE trial: a biomarker-stratified, clinical trial of treatment strategies in patients with newly-diagnosed Crohn's disease. OP01, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
2. Biasci D, et al. Gut. 2019;68(8):1386-1395.
3. Lee JC, et al. J Clin Invest. 2011;121(10):4170-4179.
4. Noor N, et al. Lancet Gastroeterol Hepatol. 2024. Feb 21:S2468-1253(24)00034-7.

Biologicals and JAK inhibitors hold promise in microscopic colitis

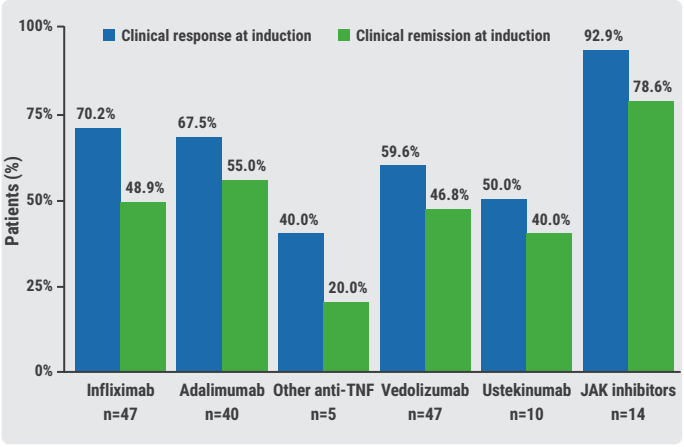
Biologic agents and small molecules appeared to be effective options in patients with microscopic colitis (MC) who were mostly budesonide-refractory or budesonide-dependent. JAK inhibitors delivered the highest clinical remission rates, although the number of patients treated with this type of small molecule was small.

"Currently, oral budesonide is the only approved therapy for patients with MC," said Dr Bram Verstockt (University Hospitals Leuven, Belgium) at the start of his presentation [1]. However, this agent has several limitations, such as a high relapse rate when tapering off of budesonide, treatment resistance, and side effects like osteopenia with long-term exposure. Dr Verstockt and colleagues performed a retrospective case series study to explore the value of biological agents and small molecules in patients with MC (n=98). The population consisted predominantly of women (86.7%) and had a median age at diagnosis of 49.1 years.

TNF inhibitors were used in 77% of the study group, mostly as a first-line advanced therapy option. "This is probably due to the easy access to these agents," added Dr Verstockt. Vedolizumab was another commonly-used therapy, used in 28% of the included patients, either in first- or second-line. Other biologicals or JAK inhibitors were only administered in a small number of patients. Clinical

response and clinical remission rates, and their definitions, are summarised in the Figure; percentages were notably high for JAK inhibitors.

Figure: Clinical response and remission rates at the end of induction therapy [1]



Clinical response: 50% reduction in stool frequency; Clinical remission: <3 stools/day or <1 watery stool/day.

"Although this was a retrospective study, the results imply that advanced therapies can significantly improve the quality-of-life of patients with MC," concluded Dr Verstockt. "The high response rate, high clinical remission rate, and promising treatment persistence rate among patients treated with JAK inhibitors encourage us to further evaluate the role of these agents in patients with MC."

1. Verstockt B, et al. Promising efficacy of biologicals and small molecules for microscopic colitis: results from a large real-life multicenter cohort. DOP79, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

Ustekinumab as alternative for anti-TNFs in HLA-DQA1*05-positive Crohn's disease

In a cohort of the ENEIDA registry, carriage of the HLA-DQA1*05 allele did not influence ustekinumab treatment outcomes in patients with Crohn's disease (CD). Therefore, the agent may be considered as an alternative to TNF inhibitors in patients with CD carrying this allele, in whom it is known that the efficacy of TNF inhibitors is compromised.

"Carriage of the HLA-DQA1*05 allele is associated with the development of anti-drug antibodies to TNF inhibitors in patients with CD, hampering the efficacy of these drugs," explained Dr Jordi Guardiola (University Hospital Bellvitge, Spain) [1–3]. "Proactive anti-TNF therapy optimisation or combining anti-TNFs with an immunomodulator are options to overcome this issue but are not feasible solutions in all patients" [4]. Therefore, Dr Guardiola and co-investigators evaluated the influence of HLA-DQA1*05 carriage on the IL-12/23 blocker ustekinumab treatment outcomes in patients with active CD through a multicentre, retrospective, cohort study (n=204; HLA-DQA1*05 carriage n=85) [1].

There was no association between carriage of the HLA-DQA1*05 allele and time to loss of response to ustekinumab therapy (HR 0.99; 95% CI 0.6–1.7; P=0.99). "This result was consistent, irrespective of concomitant use of an immunomodulator or the number of previous biologicals that had been administered," added Dr Guardiola. Similarly, the persistence of ustekinumab treatment was comparable for HLA-DQA1*05 carriers and non-carriers (HR 0.92; 95% CI 0.5–1.8; P=0.81). Finally, clinical and biological remission rates at week 26 and week 52 were identical for both patient groups.

"First-line treatment with ustekinumab rather than TNF inhibitors may be considered in HLA-DQA1*05-positive patients with CD, particularly when the use of a concomitant immunosuppressant is contraindicated and proactive therapeutic drug monitoring is not feasible," decided Dr Guardiola.

1. Guardiola J, et al. Effect of the HLA-DQA1*05 allele on the efficacy of Ustekinumab in patients with Crohn's Disease. Multicenter study based on the ENEIDA registry of GETECCU. OP37, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
2. Sazonovs A, et al. Gastroenterology. 2020;158:189-199.
3. Solitano V, et al. Clin Gastroenterol Hepatol. 2023;21(12):3019-3029.
4. Bergstein S, et al. J Crohn's and Colitis. 2023;17; Issue Supplement_1:i148-i150.

How effective is dose escalation of biologicals in IBD?

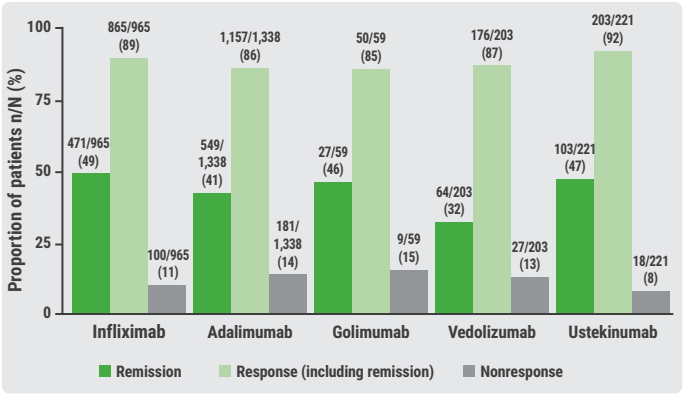
Dose escalation of biologic therapies appeared to be an effective strategy to recapture clinical response and clinical remission in patients with inflammatory bowel disease (IBD), results of the RAINBOW-IBD study of the ENEIDA registry showed.

"Biologic agents have proven effective in patients with IBD, but many patients require dose escalation after some time, mostly due to a loss of response," said Dr Cristina Rubín de Célix (University Hospital La Princesa, Spain). The current retrospective, multicentre, non-interventional study aimed to evaluate the frequency and effectiveness of dose escalations of the anti-TNF agents infliximab, adalimumab, and golimumab, the α4β7 integrin inhibitor vedolizumab, and the IL-12/23 blocker ustekinumab.

Of the 19,720 patients with IBD treated with biologic agents, 5,096 (26%) needed dose escalations. "At 1 year, approximately 15% of the patients on anti-TNF agents received a dose escalation; 25–31% of the patients needed a dose escalation at 5 years," expressed Dr Rubín de Célix. The corresponding rates for vedolizumab were 19% and 33%, and 17% and 37% for ustekinumab.

Clinical remission was achieved in 32–49% of patients receiving dose escalations, depending on the administered agent (see Figure). Recapture of clinical response was high, at 85–92%, across all treatment groups. In patients who regained response following dose escalation, 82–93% were still on treatment at 1 year and 66–88% of patients were still on the dose-escalated treatment at 2 years. Lastly, prior biologic experience, IBD type, and a short evolution of IBD were noted as predictive factors of treatment discontinuation after dose escalation.

Figure: Effectiveness of dose escalation of biologic therapies in IBD [1]



"Thus, dose escalation of biologic therapies is an effective strategy to recapture clinical response and remission in patients with IBD," concluded Dr Rubín de Célix.

1. Rubín de Célix C, et al. Frequency and effectiveness of dose escalation of biologic therapy in inflammatory bowel disease: the RAINBOW-IBD study of ENEIDA. DOP75, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

Make Way for JAK Inhibitors

Promising data for JAK inhibitors in Crohn's disease from phase 2 trial

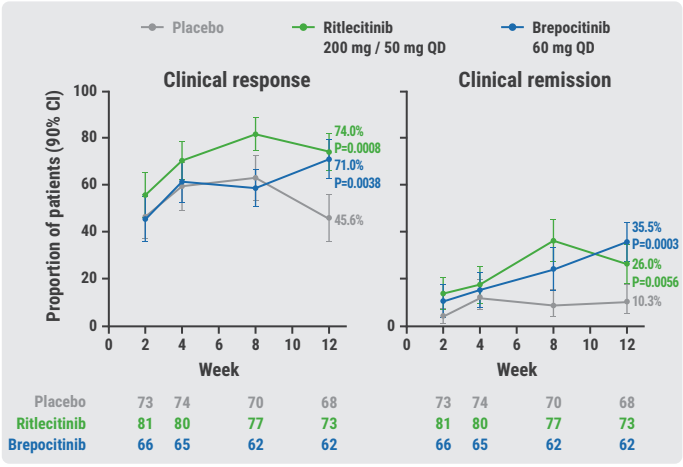
Both ritlecitinib and brepocitinib were associated with improved efficacy outcomes compared with placebo in patients with moderate-to-severe Crohn's disease (CD). The JAK inhibitors were generally safe and well tolerated in the phase 2 PIZZICATO trial.

"JAK and TEC family pathways are implicated in the pathogenesis of CD through the regulation of pro-inflammatory cytokine signalling and CD8-positive T-cell cytotoxicity," explained Dr Séverine Vermeire (University Hospitals Leuven, Belgium) [1].

The double-blind, phase 2 PIZZICATO trial (NCT03395184) tested the JAK3/TEC family inhibitor ritlecitinib and the TYK2/JAK1 inhibitor brepocitinib in patients with moderate-to-severe CD (n=244). PIZZICATO used an umbrella trial design, which allows more than one treatment to be tested in the same trial protocol. Approximately half of the participants were randomised 2:1 to ritlecitinib or a placebo and the other half was randomised 2:1 to brepocitinib or a placebo. After 12 weeks, all participants received a maintenance dose of either ritlecitinib or brepocitinib up to week 52. The primary outcome measure was the Simple Endoscopic Score for Crohn's Disease (SES-CD) 50 at week 12.

At week 12, treatment with brepocitinib (33.8%) and treatment with ritlecitinib (27.2%) resulted in higher SES-CD 50 rates than treatment with placebo (12.8%; P=0.0012 and P=0.012,

Figure: Clinical response and remission in PIZZICATO [1]



Clinical response: ≥30% reduction from baseline in abdominal pain or stool frequency, neither worse than baseline; Clinical remission: stool frequency ≤1.5 and abdominal pain ≤1, neither worse than baseline.

respectively). Similar results were observed for Clinical Disease Activity Index (CDAI) 100 response rates, CDAI remission (i.e. CDAI<150) rates, and outcomes related to abdominal pain or stool frequency (see Figure on the previous page).

"Both ritlecitinib and brepocitinib were generally well tolerated and their safety profiles were consistent with previous publications on these agents," said Dr Vermeire. Treatment-emergent adverse events that occurred in ≥5% of the participants in the brepocitinib group were headache, abdominal pain, acne, and lymphopenia. In the ritlecitinib arm, only COVID-19 was reported in ≥5% of the participants.

"Ritlecitinib and brepocitinib resulted in a statistically significant improvement in SES-CD 50 and met the primary endpoint in the 12-week induction period, compared with placebo, in participants with CD," concluded Dr Vermeire.

1. Vermeire S, et al. Oral ritlecitinib and brepocitinib in patients with moderate to severe active Crohn's disease: data from the PIZZICATO umbrella study. OP09, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

U-ENDURE long-term extension: sustained efficacy of upadacitinib in Crohn's disease

The efficacy of upadacitinib was maintained over 2 years of treatment in patients with moderately to severely active Crohn's disease (CD), results of the U-ENDURE long-term extension study showed. According to the authors, no new safety issues were identified.

In the U-ENDURE trial, upadacitinib maintenance therapy, at either a 15 mg or 30 mg dose, outperformed placebo across clinical and endoscopic endpoints over 52 weeks [1]. Participants who completed the 52-week maintenance period could continue in the long-term extension study of U-ENDURE. In total, 173 participants on upadacitinib 30 mg, 107 participants on upadacitinib 15 mg, and 89 participants on placebo entered the long-term extension study. Dr Geert D'Haens (Amsterdam University Medical Centers, the Netherlands) presented the findings [2].

After 48 weeks, stool frequency/abdominal pain score (SF/APS) clinical remission rates were sustained in the 30 mg arm (80.3% at week 0 vs 76.7% at week 48), the 15 mg arm (78.3% vs 82.1%), and in the placebo arm (73.0% vs 70.2%). Similar outcomes were observed for Crohn's Disease Activity Index (CDAI) clinical remission rates and clinical response rates. Looking at endoscopic response, rates were sustained in the 30 mg arm (66.5% vs 66.7%) and the 15 mg arm (59.6% vs 65.8%), but appeared to have dropped somewhat in the placebo arm (32.9% vs 25.0%).

Although there were no new safety issues after up to 204 weeks of upadacitinib exposure, Dr D'Haens highlighted some events. "Herpes zoster was observed in 4.3% and 1.7% of the participants in the 30 mg arm and 15 mg arm, respectively. Therefore, it is imperative to vaccinate your patients," he recommended. "Next to that, we noticed some dose-dependent lymphopenia, with 6.4% in the lower dose arm and 9.0% in the higher dose arm, and some hepatic disorders, with 6.9% in the 15 mg arm and 9.7% in the 30 mg arm." Dr D'Haens added that these events were generally no reason to discontinue the treatment.

Overall, clinical and endoscopic outcomes were maintained with prolonged treatment with upadacitinib in patients with CD, without revealing new safety issues.

1. Loftus EV, et al. N Engl J Med 2023;388:1966-1980.
2. D'Haens G, et al. Efficacy and safety of Upadacitinib in patients with moderately to severely active Crohn's disease: results from the U-ENDURE long-term extension. OP10, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

TRIUMPH: Tofacitinib as rescue option for acute severe ulcerative colitis

Tofacitinib appeared to be an effective treatment for steroid-refractory patients with acute severe ulcerative colitis (UC), displaying a swift onset of action and a high clinical response rate in bio-naïve and bio-experienced patients in the phase 2 TRIUMPH trial. The authors suggest that tofacitinib could be a treatment option for hospitalised patients with severe UC.

"Currently, cyclosporine and infliximab are the rescue therapies for patients with acute severe UC," stated Dr Neeraj Narula (McMaster University, Canada) [1]. "Cyclosporine delivers efficacy in the short-term but may lead to complications in the long-term [2]. Infliximab is a good option but not in patients who are exposed to prior TNF inhibitors." The JAK inhibitor tofacitinib may be an alternative option for this patient population. It displayed clinical improvements within 3 days in patients with moderate-to-severe UC and proved efficacious in patients with prior exposure to anti-TNF agents or other biologic therapies [3].

In the TRIUMPH study (NCT04925973), 24 hospitalised patients with severe steroid-refractory UC were treated with tofacitinib to assess its utility in this setting. "Of these 24 patients, 8 had failed on a prior biologic therapy," mentioned Dr Narula, who presented the results of a 26-week interim analysis [1]. The primary endpoint was clinical response at day 7.

The clinical response rate at day 7 was 58% and exactly one-third of the included patients were in steroid-free clinical remission at week 26. Moreover, 33.3% of them displayed endoscopic improvement after a half year of follow-up. "The mean time to response was 2.4 days and no new safety issues were identified," added Dr Narula.

"With a rapid onset of action and a high clinical response rate in both bio-naïve and bio-experienced patients, tofacitinib should be considered for hospitalised patients with acute severe UC," concluded Dr Narula.

1. Narula N, et al. Tofacitinib for hospitalized acute severe ulcerative colitis (TRIUMPH): interim analysis to 26 weeks. DOP46, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
2. Lichtiger S, et al. N Engl J Med 1994;330(26):1841-1845.
3. Sandborn WJ, et al. N Engl J Med 2017;376(18):1723-1736.

Focus on Endoscopy, Screening, and Risk Factors

Should we screen for metabolic bone disease at IBD diagnosis?

High metabolic bone disease rates were observed among patients with newly diagnosed inflammatory bowel disease (IBD). According to the authors, the findings of this study indicate that systematic screening of these patients is warranted.

Dr Mohamed Attauabi (Copenhagen University Hospital, Denmark) and colleagues assessed the occurrence of metabolic bone disease among patients with IBD in a population-based inception cohort study called 'the IBD prognosis study' [1]. Since 2021, they have been recruiting patients with IBD from the uptake area of the Herlev and Hvidovre Hospitals in Denmark. All participants with incident IBD (n=509) were invited to a dual-energy X-ray absorptiometry (DXA) at diagnosis; 70% underwent such a DXA.

"Two groups of interest were post-menopausal women, defined as women over 51 years of age, and elderly men, defined as men over 49 years of age," added Dr Attauabi. Osteoporosis was observed in 35.7% and 28.6% of the post-menopausal women with ulcerative colitis (UC) and Crohn's disease (CD), respectively. "In the healthy post-menopausal population, this rate is 12%," stated Dr Attauabi. The corresponding rates in elderly men were 13.2% and 12.5% in those with UC and CD, and 2.6% in the healthy population of elderly men.

Dr Attauabi added that osteopenia rates were high in pre-menopausal women with UC or CD between 30 and 51 years of age (28.9%; 23.5%) as well as in younger men with UC or CD in the same age group (23.3%; 26.9%). Finally, the authors did not find any general or IBD-related risk factors that significantly influenced the risk of osteoporosis or osteopenia in this population.

"Approximately every third menopausal woman with previously untreated IBD had osteoporosis," summarised Dr Attauabi. "In elderly men with IBD, this rate was a little over 10%. In younger, newly diagnosed patients, we saw high osteopenia rates. The high incidence of metabolic bone disease among newly diagnosed patients with IBD warrants systematic screening of patients," he concluded.

1. Attauabi M, et al. Should all patients with newly diagnosed inflammatory bowel diseases be screened for metabolic bone disease? Results from a Danish population-based inception cohort study. OP38, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

Predicting relapse in ulcerative colitis with AI-assisted endoscopy

AI-assisted colonoscopy could predict long-term clinical relapse in patients with ulcerative colitis (UC) who were in clinical remission. Moreover, this novel tool was compatible with a wide range of colonoscopes.

Dr Yasuharu Maeda (Showa University Northern Yokohama Hospital, Japan; University College Cork, Ireland) and colleagues developed an AI-assisted, image-enhanced endoscopy method to assess vascular healing and predict clinical relapse in patients with UC who were in clinical remission [1]. "Although there is already an AI-assisted endoscopy tool for the prediction of histologic remission approved in Japan, this tool, called EndoBRAIN-UC, is only applicable for the Endocyto colonoscope," commented Dr Maeda [1,2]. The novel tool can be adapted to a wide range of standard colonoscopes.

The prospective cohort study at hand used the novel AI-enhanced colonoscopy model to diagnose 'vascular-healing' and predict clinical relapse based on the outcomes; 33 patients were considered to be in the 'healing' group, whereas 67 patients were considered to be in the 'active disease' group [1].

At 12 months, the relapse rate was 3.0% in the 'healing' group and 23.9% in the 'active' group (P=0.01), indicating that AI-assisted colonoscopy could identify patients at high risk of relapse. Furthermore, Dr Maeda showed that AI-enhanced colonoscopy, categorising patients according to their 'vascular-healing' status, may add to the AUC value of complete endoscopic remission for the prediction of relapse (AUC 0.65 to AUC 0.70).

"The current, novel, AI-based endoscopy system for diagnosing 'vascular-healing' identified patients with UC at high risk of relapse," decided Dr Maeda.

1. Maeda Y, et al. A novel artificial intelligence-assisted image enhanced endoscopy assesses accurately "vascular-healing" and predicts long-term clinical relapse in patients with ulcerative colitis: a prospective cohort study. OP16, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
2. Maeda Y, et al. Gastrointest Endosc. 2022;95(4):747-756.e2.

Clear case for *NUDT15* genetic testing in Asian patients with IBD

A study into the clinical utility of *NUDT15* pharmacogenetic testing showed that *NUDT15* variant carriage was associated with an increased risk of thiopurine-induced myelosuppression and severe myelosuppression. The authors made a clear case for *NUDT15* testing among East and South Asian patients with inflammatory bowel disease (IBD).

Dr Chris Roberts (University of Exeter, UK) and co-investigators evaluated the utility of *NUDT15* genotyping by assessing the link between *NUDT15* carriage and thiopurine-induced myelosuppression [1]. The research team screened 23,081 participants of the IBD BioResource and identified 239 thiopurine-exposed individuals with *NUDT15* variants and matched them with 1,570 thiopurine-exposed individuals with wildtype *NUDT15* and *TPMT*.

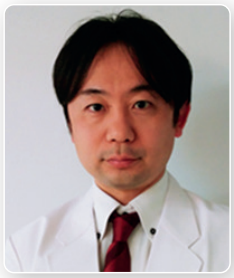
East Asians (21.7%) and South Asians (13.6%) were more likely to carry any *NUDT15* variants than Europeans (1.3%) or Africans (1.6%). Thiopurine-induced myelosuppression was documented in 78 (32.6%) individuals in the *NUDT15* carrier group and in 115 (13.7%) individuals in the *NUDT15* wildtype group (OR 3.1; 95% CI 2.2–4.3; P<0.001). "The more clinically relevant 'severe myelosuppression' was reported in 11.3% and 1.0% of the patients, disfavouring the *NUDT15* carriers (OR 13.3; 95% CI 6.2–31.6; P<0.001)," noted Dr Roberts. "Myelosuppression-related hospitalisations were documented in 2.9% and 0.1% of the patients" (OR 7.0; 95% CI 1.0–142.6; P=0.07).

Furthermore, the number needed to genotype to prevent a single case of thiopurine-associated myelosuppression was 786 in the European population but only 29 in the South Asian population. "There is therefore a clear case for *NUDT15* testing among East and South Asian individuals," argued Dr Roberts. "Also, we recommend simultaneous *NUDT15* and *TPMT* genotyping because of the severe myelosuppression that can be seen in patients who carry variants of both these genes."

Dr Roberts recommended the following thiopurine dosage for *NUDT15* carriers:

- In wildtype *NUDT15* and *TPMT*: 2.0–2.5 mg/kg/day.
- In *NUDT15* heterozygotes: dose reduction by 50% or alternative therapy.
- In *NUDT15* homozygotes or compound heterozygotes: thiopurine avoidance.
- In *NUDT15* and *TPMT* heterozygotes: thiopurine avoidance.

1. Roberts C, et al. Exploring the potential clinical utility of NUDT15 pharmacogenetic testing in clinical practice: a 'focused reverse phenotyping' study in the UK IBD Bioresource. OP11, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.



Dr Yasuharu Maeda,
MD, PhD

Meet the Trialist: Dr Yasuharu Maeda on AI-assisted endoscopy

Medicom Medical Publishers interviewed Dr Yasuharu Maeda (College of Medicine and Health, University College Cork, Ireland and Digestive Disease Center, Showa University Northern Yokohama Hospital, Japan) about his innovative research at the intersection of artificial intelligence (AI) and endoscopic imaging. His work primarily focuses on enhancing the accuracy and efficiency of diagnostic procedures for gastrointestinal diseases, with a special emphasis on inflammatory bowel diseases such as ulcerative colitis (UC).

At the 19th Congress of ECCO, Dr Maeda presented a study titled "A novel artificial intelligence-assisted Image Enhanced Endoscopy assesses accurately 'vascular-healing' and predicts long-term clinical relapse in patients with UC: a prospective cohort study" [1]. This presentation highlights his latest research findings, showcasing the potential of AI-assisted image-enhanced endoscopy in the management of UC. By accurately assessing vascular healing and predicting long-term clinical relapse, Dr Maeda's work offers hope for improved patient care and outcomes in the field of gastroenterology. Medicom contacted him to answer some questions.

Can you explain the significance of microvascular findings in managing UC and how they've traditionally been identified?

"With image-enhanced endoscopy (IEE) and magnifying endoscopy, microvascular findings on the colorectal mucosa have been observed in detail. This approach has a stronger correlation with histologic activity and long-term prognosis compared with white light endoscopy (WLE) assessment. Furthermore, it allows on-site assessment without the need for biopsy, thus reducing pathologist effort and cost compared with histology. However, special training is required to achieve high accuracy," Dr Maeda noted. "Therefore, it is not yet widely used in clinical practice."

What challenges do specialist endoscopists face in detecting inflammation in UC, and how does AI-assisted IEE address these issues?

"There are 2 main challenges," Dr Maeda said. "First, even among specialists, endoscopic scoring by conventional WLE varies widely between examiners. Secondly, there are cases where inflammatory activity remains histologically even when the patient is judged to be in remission by WLE."

"AI-assisted IEE provides an objective assessment, reduces inter-operator variability, and identifies microinflammatory findings not seen with WLE," highlighted Dr Maeda.

How does the new AI-based NBI system work, and what makes it adaptable to various commercially available endoscopes?

"When narrow-band imaging (NBI) images are acquired, 2 class classifications –Healing and Active– are the immediate output. To adapt the AI algorithm to different endoscopes, training images were collected using different commercially available endoscopes."

Could you elaborate on the concept of 'vascular healing' identified by AI and its importance in predicting UC relapse?

"Vascular findings are known to correlate with inflammatory activity." However, Dr Maeda noted, "vascular atypia may persist even when the patient appears to be in remission on WLE. This is the same as histologic inflammation. It has been reported in the past that residual vascular atypia is a risk factor for UC recurrence. The AI assists the endoscopist by providing an objective diagnosis."

Curious?
Continue reading this interview online.

1. Maeda Y, et al. A novel artificial intelligence-assisted Image Enhanced Endoscopy assesses accurately "vascular-healing" and predicts long-term clinical relapse in patients with ulcerative colitis: a prospective cohort study. Abstract OP16, ECCO 2024, 21–24 February, Stockholm, Sweden.

HELIOS: HD-WLE can yield similar neoplasia detection rates as HD-CE

High-definition white light endoscopy with segmental re-inspection (HD-WLE with SR) was non-inferior to dye-based high-definition chromoendoscopy (HD-CE) for the detection of colorectal neoplasia in patients with inflammatory bowel disease (IBD) in the HELIOS trial.

"Although dye-based HD-CE is considered the gold standard for detecting colorectal neoplasia in patients with IBD, the uptake remains fairly low in clinical practice, likely due to issues of practicality, cost, and training," said Dr Maarten te Groen (Radboudumc, the Netherlands) [1]. "Therefore, HD-WLE is more frequently used in clinical practice." He explained that it remains unknown whether the advantage of HD-CE comes from enhanced contrast or from longer withdrawal times. Evidence in the non-IBD population indicates that longer withdrawal times are correlated with higher colorectal neoplasia detection rates [2]. "We hypothesised that HD-WLE with matched withdrawal times may yield similar neoplasia detection rates as HD-CE," Dr te Groen expressed [1].

The randomised-controlled HELIOS trial (NCT04291976) compared 3 endoscopy techniques for the outcome measure of colorectal neoplasia in patients with IBD. HD-WLE with SR was tested against HD-CE for non-inferiority and compared with single-pass HD-WLE for superiority. The trial randomised 666 adult patients with IBD who were scheduled for endoscopic surveillance 2:2:1 to HD-WLE with SR, HD-CE, or single-pass HD-WLE.

The colorectal neoplasia detection rate was 10.3% in the HD-WLE with SR arm and 13.1% in the HD-CE arm. The lower bound of the 95% confidence interval (-7.8%) did not cross the non-inferiority border of -10.0%; therefore, non-inferiority of HD-WLE with SR to HD-CE was demonstrated in this population ($P_{non\text{-}inferiority}$<0.01). The colorectal neoplasia detection rate was 6.1% in the single-pass HD-WLE arm; the difference of 4.1% with the HD-WLE with SR arm was not statistically significant (95% CI -2.2 to 9.6%; P=0.19). Finally, the median withdrawal times were 19, 26, and 15 minutes in the HD-WLE with SR, HD-CE, and single-pass HD-WLE arms, respectively.

"HD-WLE with SR is non-inferior to HD-CE but not superior to single-pass HD-WLE," concluded Dr te Groen. He argued that the lower-than-expected colorectal neoplasia rates and subsequent lower power of the trial could be an explanation for the result of the superiority analysis. "Also, the results indicate that the benefit from HD-CE is mostly explained by the longer withdrawal time and not necessarily by enhanced contrast."

1. Te Groen M, et al. High-definition white light endoscopy with segmental re-inspection is non-inferior to dye-based chromoendoscopy in inflammatory bowel disease: the randomized controlled HELIOS trial. OP15, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
2. Shaukat A, et al. Gastroenterology. 2015;149(4):952-957.

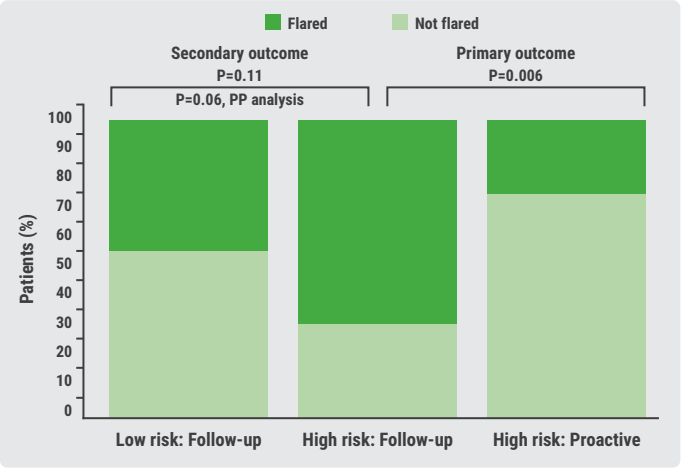
CURE-CD: Capsule endoscopy-guided proactive treatment leads to fewer relapses in Crohn's disease

A capsule endoscopy-guided treatment strategy led to fewer relapses than standard-of-care in patients with quiescent Crohn's disease (CD) who were displaying high-risk video capsule endoscopy (VCE) features at baseline in the CURE-CD trial.

"Lewis scores of 350 and higher on VCE identify patients with a high risk of flares within the next 2 years, with a better predictive accuracy than faecal calprotectin," explained Dr Shomron Ben-Horin (Tel-Aviv University, Israel) [1,2]. The current, prospective, randomised-controlled CURE-CD trial (NCT03555058) evaluated the efficacy of VCE as a guidance tool for patients with CD and small bowel involvement in clinical remission (n=60) [1].

At baseline, participants received VCE and those with a Lewis Score of 350 or higher (n=40) were randomised 1:1 to standard-of-care or to capsule endoscopy-guided proactive treatment for 24 months. "The proactive treatment regimen included biologic dose-escalation and initiating or swapping a biologic treatment," added Dr Ben-Horin. Low-risk participants (n=20) continued on standard-of-care. The primary endpoint was the rate of relapse/disease complications in the high-risk population.

Figure: Main results of the CURE-CD trial at 24 months [2]



At 24 months, the clinical flare rate was 25% in the experimental arm and 70% in the control arm, meeting the primary endpoint (OR 0.14; 95% CI 0.04–0.57; P=0.006). "We also noted a trend towards fewer relapses in the low-risk standard-of-care group compared with the high-risk standard-of-care group (45% vs 70%; P=0.11), which was a secondary endpoint of the trial" (see Figure).

"High-risk patients with CD, as defined by baseline VCE scores, benefitted from a proactive treat-to-target strategy for the prevention of disease exacerbations," concluded Dr Ben-Horin.

1. Ben-Horin S, et al. Capsule endoscopy-guided proactive treatment versus standard care in patients with quiescent Crohn's disease: the CURE-CD randomized controlled trial. DOP29, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
2. Ben-Horin S, et al. Lancet Gastroenterol Hepatol. 2019;4(7):519-528.

Sharp Surgical Solutions

Extended mesenterectomy or mesenteric-sparing surgery in Crohn's disease?

Extended mesenterectomy did not outperform mesenteric-sparing surgery in patients with Crohn's disease (CD) undergoing primary ileocolic resection, data from the international SPICY trial displayed. Therefore, the authors advise to perform mesenteric-sparing surgery in these patients.

"Post-operative recurrence of CD is the standard and not an exception," stated Dr Eline van der Does de Willebois (Amsterdam University Medical Centers, the Netherlands) [1]. "We should therefore aim to investigate options to prevent post-operative recurrence of CD following ileocolic resection." It is somewhat unclear whether an extended mesenterectomy or a mesenteric-sparing approach yields better outcomes. It has been suggested that the mesentery could be a driver of disease, whereas others think that the mesentery might be a protective contributor [2,3].

To gain an evidence-based perspective on this matter, the double-blinded, international SPICY trial (NCT04538638) randomised 139 patients with CD undergoing primary ileocolic resection 1:1 to extensive mesenteric resection following the lower border of the ileocolic trunk or mesenteric-sparing ileocolic resection, as is currently advised by guidelines [1]. The primary endpoint was endoscopic recurrence at 6 months after the procedure, defined as a modified Rutgeerts score ≥i2b.

Endoscopic recurrence was reported in 42.4% of the participants in the extended mesenterectomy arm and in 43.1% of the participants in the mesenteric-sparing arm, revealing no clear difference between both arms. Dr van der Does de Willebois added that anastomotic leakage was numerically more common in the extended mesenterectomy arm (7.6% vs 1.5%; P=0.21).

"Since extended mesenterectomy is not superior to a mesenteric-sparing approach and anastomotic leakage may occur more frequently in patients undergoing extended mesenterectomy, we opt for the mesenteric-sparing approach in patients with CD undergoing primary ileocolic resection," concluded Dr van der Does de Willebois.

1. Van der Does de Willebois E, et al. Mesenteric sparing or extended mesenterectomy in primary ileocolic resection for Crohn's disease: results of an international randomised controlled trial. OP19, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.
2. Coffey CJ, et al. J Crohns Colitis. 2018;12(10):1139-1150.
3. Ha CWY, et al. Cell. 2020;183(3):666-683.e17.

Similar outcomes for Kono-S and side-to-side anastomosis in Crohn's terminal ileitis

Kono-S and side-to-side anastomosis appeared to elicit comparable endoscopic recurrence rates, anastomotic strictures rates, and post-operative complication rates in patients undergoing ileocecectomy for Crohn's terminal ileitis, preliminary data of a randomised trial revealed.

Dr Koianka Trencheva (Weill Cornell Medicine, NY, USA) and her research team aimed to compare Kono-S and side-to-side anastomosis following ileocecectomy for Crohn's terminal ileitis [1]. In a multicentre trial (NCT03256240), 288 patients were randomised 1:1 to one of these interventions. The endoscopic recurrence rate at 3–6 months post-surgery was the main outcome measure.

The 3–6-month endoscopic recurrence rates were 25.9% and 27.8% in the Kono-S arm and side-to-side arm, respectively (P=0.78). "We noticed that the length of the surgical procedure was approximately 20 minutes longer in the Kono-S arm (mean 154 vs 132 minutes; P=0.39)," added Dr Trencheva. Furthermore, post-op complication rates and anastomotic stricture rates (3.0% vs 2.6%; P=1.00) were comparable for both arms.

"At 3–6 months follow-up, Kono-S and side-to-side anastomosis yield similar outcomes for patients undergoing ileocecectomy for Crohn's terminal ileitis," concluded Dr Trencheva.

1. Trencheva K, et al. Postoperative endoscopic recurrence after resection of Crohn's terminal ileitis with Kono-S or side-to-side functional end anastomosis: results of a multicenter prospective randomized trial. OP20, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

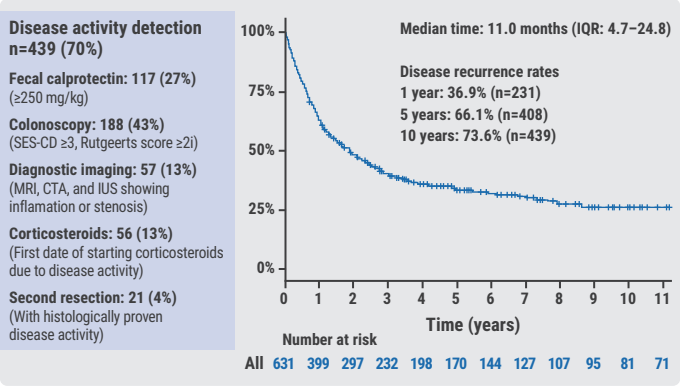
Risk factors for re-resection in Crohn's disease revealed

In patients with Crohn's disease (CD), a primary resection with colon involvement and an isolated small bowel resection were associated with an increased risk of re-resection, compared with patients who received ileocecal resection, results of a population-based study indicated. Furthermore, administering biologic therapy may reduce the risk of re-resection in subgroups of patients.

"In Crohn's disease, there is a decline in resection rates but not in re-resection rates," expressed Dr Anja Poulsen (Copenhagen University, Denmark) [1]. The current population-based study aimed to describe the re-resection rates for patients with CD and to identify disease-modifying factors and risk factors associated with disease recurrence and re-resection. The authors identified 631 Danish patients who had undergone primary resection for CD [2].

"The cumulative risk of re-resection due to disease activity was 3.6% at 1 year, 10.1% at 5 years, and 14.1% at 10 years," stated Dr Poulsen. Also, the median time from primary resection to disease recurrence was 11.0 months, with corresponding disease recurrence rates of 36.9% at 1 year, 66.1% at 5 years, and 73.6% at 10 years (see Figure). Next, Dr Poulsen mentioned that the most commonly performed resections were a 'simple ileocecal resection' (60.0%), an 'ileocecal resection with colon ascendens included' (10.0%), and a 'more extensive ileocecal resection' (7.8%). "Importantly, patients undergoing a simple ileocecal resection as primary surgery had a re-resection risk of 6.3%, whereas those who underwent a small bowel resection or had a part of the colon included in the primary resection had re-resection risks of 14.3% and 19.0%, respectively. Furthermore, there was a reduced risk of re-resection in patients with B2 or B3 disease types who received biological therapy within the first year after primary resection (B2: HR 0.56; 95% CI 0.34–0.93; P=0.026; B3: HR 0.31; 95% CI 0.15–0.64; P=0.002). Finally, prophylactic biological therapy after a primary ileocecal resection appeared to reduce the risk of post-operative disease recurrence and re-resection (HR 0.58; 95% CI 0.34–0.99; P=0.047).

Figure: Time from primary resection to disease recurrence [2]



The current study provided insights into re-resection rates and associated risk factors in patients with CD. Disease phenotype, involved segments in the primary resection procedure, and biological therapies appear to influence the risk of disease recurrence and re-resection in these patients.

1. Tsai L, et al. Clin Gastroenterol Hepatol. 2021;19(10):2031-2045.e11.
2. Poulsen A, et al. Risk of disease recurrence and re-resections in Crohn's disease patients undergoing primary bowel resection: a population-based study. OP34, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.

ADMIRE-CD-II: Darvadstrocel does not meet primary endpoint in complex peri-anal fistula

Darvadstrocel treatment did not lead to better outcomes than placebo in patients with complex peri-anal fistula (CPF) and Crohn's disease (CD) in the phase 3 ADMIRE-CD II trial.

Darvadstrocel, a suspension of expanded adult, adipose-derived, allogeneic mesenchymal stem cells, was assessed as a potential therapy for patients with CPF and CD in a global phase 3 study, called ADMIRE-CD-II (NCT03279081).

Participants (n=568) were randomised 1:1 to a single dose of darvadstrocel or a placebo. Clinical and MRI assessment at week 24 was the primary outcome measure, of which the results were shared by Dr Zuzana Serclova (Hořovice Hospital, Czech Republic) [1].

At week 24, the combined remission endpoint was met by 46.3% of the participants in the placebo arm and by 48.8% of the participants in the experimental arm (Δ2.4; 95% CI -5.8 to 10.6; P=0.57). At week 52, there was still no difference between the groups for this endpoint of combined remission (39.7% vs 41.0%; Δ1.3; 95% CI -6.8 to 9.3; P=0.76). Finally, darvadstrocel was well tolerated and the treatment arms were comparable regarding safety events.

"Treatment of CPF with a single dose of darvadstrocel showed numerically higher response rates for key efficacy endpoints compared with placebo, but these differences were not clinically meaningful or statistically significant," concluded Dr Serclova.

1. Serclova Z, et al. Efficacy and safety of darvadstrocel treatment in patients with complex perianal fistulas and Crohn's disease: results from the global ADMIRE-CD II phase 3 study. OP18, 19th Congress of ECCO, 21–24 February 2024, Stockholm, Sweden.