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PEER-REVIEWED CONFERENCE REPORT

Gut Microbiome as Treatment Target

Response to faecal microbiota transplantation in UC patients was associated with an increase in mucosal gut-homing Treg cells and butyrate metabolism, and a reduction in anti-microbial and pro-inflammatory pathways.

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Study Results of Experimental Therapies

The majority of agents currently in phase 2 and phase 3 trials are expected to reach the market by 2025, effectively doubling the armamentarium at the disposal of clinicians.

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Head-to-Head Comparison of Treatments

As efficacy and safety of UC biologics are being compared in several head-to-head, controlled, comparison trials, the Italian AURORA study suggests using infliximab originator as a reference drug.

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Editor Dr Marjolijn Duijvestein, Amsterdam UMC, the Netherlands

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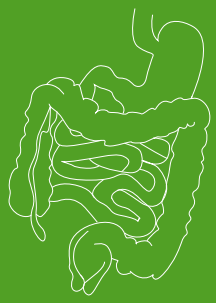

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Letter from the Editor

Dr Marjolijn Duijvestein

Dear Reader,

Much has changed since the 15th Congress of ECCO, as at that moment the COVID-19 outbreak seemed far away, but by now the pandemic is affecting all our daily life and work activities. However, I do want to take you back to a sunny Vienna, as the ECCO Congress with the theme "IBD beyond 2020" was very successful. More than 7,000 participants from 102 countries attended the meeting, either to be educated or to present their latest work and interact with IBD interested colleagues from around the world. With great pleasure we hereby share the highlights presented in Vienna February this year: new insights in modifying the gut microbiome as a treatment target, first study results of experimental studies, long term results of treatment strategies and real-world comparison analysis, as well as multi-omics and big data results of (global) consortia.

In his letter of invitation, Silvio Danese (past-president) states "Think global and not local". Many of the results presented at ECCO were the result of collaborations around the globe. By joining efforts much more is and becomes possible. To circle back to the COVID-19 pandemic I realise that this motto is even more than ever actual. A COVID-19 Taskforce composed of ECCO members keeps the IBD community updated on the ECCO website and IBD clinicians worldwide are encouraged to report all cases of COVID-19 in their IBD patients trough and international registry which aims to rapidly define and report the impact of COVID-19 on patients with IBD (https://covidibd.org/).

Last but not least, please stay healthy, take care of yourself and one another. I am looking forward to meet you next year in Berlin.

Marjolijn Duijvestein

Biography

Marjolijn Duijvestein works as a gastroenterologist at the IBD center of Amsterdam UMC, merged in 2018 from Academic Medical Center (AMC) and the VU University Medical Center. In 2012 she obtained her PhD at Leiden University and was trained as a gastroenterologist specialised in IBD disease at the AMC. As part of her training, she gained experience at the University of California San Diego (UCSD, USA) and performed an internship at Robarts Clinical Trials, an academic research organisation dedicated to drug development for IBD. Her clinical activity and research is focused on IBD, in particular clinical and translational research.

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

Gut Microbiome as Treatment Target

Response to faecal microbiota transplantation in UC

In a substudy of STOP-Colitis, response to faecal microbiota transplantation (FMT) in ulcerative colitis (UC) patients was associated with a significant increase in mucosal gut-homing Treg cells and butyrate metabolism, along with a reduction in Th17 cells and multiple anti-microbial and pro-inflammatory pathways [1].

STOP-Colitis was a prospective, open-label pilot study of FMT in UC. In a substudy, changes in host colonic mucosal immune cell subsets and gene expression following FMT were explored. Participants received 8 FMT infusions over 8 weeks; of 17 patients, 12 completed 8 weeks of FMT per protocol.

Response, defined by a reduction in Mayo score, was seen in 8 of 12 patients (67%). As first author Dr Mohammed Quraishi (University Hospital Birmingham, UK) explained, FMT responders showed a significant increase in Treg cells (Δ 5.02%; P<0.01), especially in effector-memory Treg cells (Δ 12%; P<0.001) and gut-homing Treg cells (Δ 18.55%; P<0.01). Immunophenotyping of peripheral blood mononuclear cells revealed a significant increase in IL-10 producing CD4 cells (Δ 2.16%; P=0.04), suggesting induction of peripheral immune tolerance which is preferentially compartmentalised to the colonic mucosa. Responders also had a significant reduction in mucosal Th17 cells (Δ −7.61%; P=0.017), IL-17 producing CD4 cells (Δ −7.69%; P=0.05), and CD8 cells (Δ -5.18%; P=0.04). Additionally, response was associated with a significant downregulation of host antimicrobial defence response, and with a significant upregulation of butyrate and propionate (2 short-chain fatty acids) metabolic pathways.

In another study, Dr Lasha Gogokhia (Weill Cornell Medicine, New York, USA) and colleagues attempted to unravel the mechanisms of clinical response to FMT by identifying a distinct, immune-reactive, core transferable microbiota [2]. This study provides a framework for the rational selection of immune-reactive microbiota for microbial therapy in inflammatory bowel disease (IBD). They used samples from their pilot FMT study in UC patients responsive to a single delivery of high-diversity faecal microbiota preparation [3]. To define the core transferable microbiota, metagenomic sequencing of donor, recipient, and 4-week post-FMT faecal samples was performed. To define the transferable immune-reactive microbiota (TIM), IgA-sequencing was also performed on these samples. Using a pre-clinical mouse model of colitis, the mechanistic impact of these TIM in shaping mucosal immunity and in guiding the response to UC was defined.

Results showed distinct TIMs in responders mediating iTreg protection. These TIM were found to induce IgA in a T-cell independent manner. TIM induction of IL-10 regulated both T-cell and non-T-cell mediated protection.

1. Quraishi MN, et al. ECCO-IBD 2020, OP09.
2. Gogokhia L, et al. ECCO-IBD 2020, OP40.
3. Jacob V, et al. Inflamm Bowel Dis. 2017;23(6):903-11.

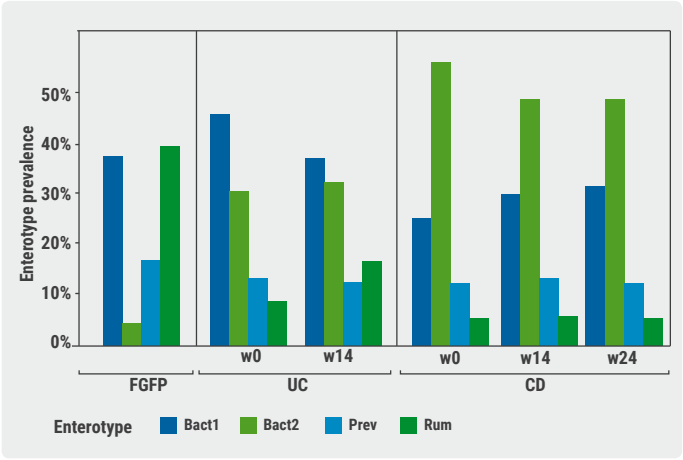
Impact of biologicals on faecal microbiota

The longitudinal impact of treatment with biologicals on the inflammatory burden and faecal microbiota in patients with Crohn's disease (CD) and ulcerative colitis (UC) was studied. Biologicals resulted in a decrease in inflammation as reflected by faecal calprotectin (FCP) levels and an increase in microbial richness, but not in a shift in enterotypes [1].

At a tertiary referral centre, faecal samples were analysed of 349 patients with inflammatory bowel diseases (IBD; 112 UC, 237 CD) initiating a TNF inhibitor, vedolizumab, or ustekinumab between 2010 and 2019. Samples were collected at week 0, 14, and 24. The results showed a high diversity in faecal microbiota profiles, with samples classified into all 4 enterotypes: Bact1, Bact2, Prev, and Rum. Bact2 was 5- to 10-fold more prevalent in CD and UC patients compared with controls (see Figure). The variation in faecal microbiota composition was explained by diagnosis, timepoint, age, gender, and faecal moisture on multivariate analysis. The full model only explained 2.85% of the microbiota variation.

Treatment was associated with a significant decrease in FCP concentrations, along with a significant increase in cell counts. Bact2 prevalence did not significantly change during treatment. Treatment response was not significantly predicted by microbiota-associated variables (enterotype, cell counts, and faecal moisture), but only by treatment-associated variables (week of treatment, P<0.0001; diagnosis,

Figure. Enterotype prevalence in an average population cohort (Flemish Gut Flora Project: FGFP) and in UC and CD cohorts at week 0, 14, and 24 of treatment with TNF inhibitor, vedolizumab, or ustekinumab confounded [1]



Bact1, *Bacteroides1*; Bact2, *Bacteroides2*; Prev, *Prevotella*; Rum, *Ruminococcus*; UC, ulcerative colitis; CD, Crohn's disease

P=0.0005; and timepoint, P=0.0073). Baseline samples were associated with higher FCP levels. This suggests that the response time of the microbiota to treatment is longer than the host inflammatory response.

1. Caenepeel C, et al. ECCO-IBD 2020, OP20.

Bioactives produced by gut bacteria to modulate immune response

An anaerobic culturing and NF-κB reporter assay system allowed for the rapid identification of bacteria producing immunomodulatory bioactives. The investigators think this may lead to the development of novel therapeutics [1].

NF-κB is a protein complex that controls transcription of DNA, cytokine production, and cell survival. In the study, the NF-κB suppressive effects of culture supernatants from 23 different isolates were tested on colonic epithelial cell lines. Suppressive culture supernatants were also tested on human-derived colonic organoids from inflammatory bowel disease (IBD) patients and healthy controls, and IL-8 expression was measured. Furthermore, culture supernatants from one specific NF-κB-suppressive *Clostridium* strain (AHG0001) was also tested in a spontaneous colitis mouse model *in vivo*.

Culture supernatants from 5 of 23 screened isolates significantly suppressed NF-κB activation. The selected culture supernatants also suppressed IL-8 secretion in peripheral blood mononuclear cells and gut organoids from both UC and CD patients, as well as healthy controls, with notable individual variation. Culture supernatants from AHG0001 reduced disease activity, improved histologic inflammation, and reduced the pro-inflammatory gene expression in the colitis mouse model. The authors concluded that their *in vivo* and *ex vivo* testing using a spontaneous colitis model and patient-derived organoids demonstrates the potential of bacterial-based therapeutics.

1. Giri R, et al. ECCO-IBD 2020, OP36.

Big Data Analysis

Multi-omics help describe CD phenotypes

By using integrated signature profiles generated from multiple 'omic' datasets, molecular mechanisms were identified which could potentially describe Crohn's disease (CD) phenotypes, like the occurrence of perianal disease [1].

Dr Bram Verstockt (University Hospital Leuven, Belgium) presented the results of this multi-omic data integration with network analysis. He explained that the molecular mechanisms which orchestrate the heterogeneity of CD are poorly understood.

In a discovery cohort of 98 CD patients, 576 unique proteins were measured in blood. All patients were also genotyped. The 2 resulting datasets were then integrated using an innovative algorithm called Multi-Omics Factor Analysis (MOFA). From this analysis, 5 so-called latent factors (LFs: representative variables capturing the sources of variation in omic datasets) associated with at least 1 clinical phenotype were identified. Clustering patients along LFs achieved meaningful separation of clinical phenotypes like perianal penetrating disease.

The top-ranking proteins associated with perianal disease were involved in inflammatory pathways and autophagy, or were already known to be implicated in CD. Dr Verstockt: "Many of the genes encoding these proteins are significantly dysregulated in draining perianal fistula, as compared to paired rectal mucosa, in independent patients. The majority of the differentially expressed serum proteins (77.8%) could be validated in an independent cohort of 88 newly diagnosed CD patients". Seven mutations mapped to transcription factors (*SMAD3*, *BACH2*) and post-translational regulators (such as *IFNGR2*, *IL10*, *IL2RA*, *SLC2A4RG*, and *ZMIZ1*) could potentially regulate perianal disease pathophysiology and could thus be considered novel drug targets. Dr Verstockt added that network analysis can also highlight potential repurposing of already existing drugs in other diseases.

In another study, an integrated multi-omics data analysis revealed microbiome-driven proteolysis as a contributing factor to the severity of ulcerative colitis (UC) disease activity. Certain members of the microbiome, such as *Bacteroides vulgatus*, may contribute to exacerbating disease activity in UC through protease activity. *In vivo* and *in vitro* experiments provide evidence that bacterial protease inhibition may be a novel therapeutic approach in UC [2].

A third multi-omics analysis revealed specific bio-geographical and functional characteristics in inflammatory bowel disease (IBD) intestinal mucosa. The results provide a unique and comprehensive cell map of IBD in a location-specific context, potentially shedding light upon unexplained clinical phenomena [3]. For example, an upregulated IL-6 pathway in Treg cells was recognised as sigmoid-specific in UC patients, which may help explain colonic perforations associated with anti-IL-6R treatment. The results may allow one to tailor therapies to affected areas to improve treatment efficacy.

1. Sudhakar P, et al. ECCO-IBD 2020, OP15.
2. Mills R, et al. ECCO-IBD 2020, OP31.
3. Maimon N, et al. ECCO-IBD 2020, OP33.

The positive impact of genetic data on drug development

In a presentation about the International IBD Genetics Consortium (IIBDGC), Prof. Séverine Vermeire (University Hospital Leuven, Belgium) explained the focus and achievements of this consortium, which is open to any group that wishes to join.

By collecting large datasets from countries from all over the world, the IIBDGC unravelled a total of about 240 significant inflammatory bowel disease (IBD)-associated single-nucleotide polymorphisms (SNPs) in multiple large genome-wide association studies (GWAS). This has yielded some 200 IBD loci, Prof. Vermeire explained. The newly identified loci have helped to much better understand the roles of the innate and acquired immune systems in the pathophysiology of IBD.

Prof. Vermeire also highlighted the importance of genetic data on the development of new drugs. She noted that >25% of drugs that enter the clinical development stage fail to reach the market due to inefficacy. Growing insights in disease susceptibility genes may affect selection of drug targets and indications. The proportion of drugs with direct genetic support increases significantly across the development pipeline, from 2% at the preclinical stage to 8.2% for approved drugs. Prof. Vermeire: "Selecting genetically supported targets can double success rate in clinical trials". She invited any group that wishes to join the IIBDGC consortium to apply. Minimum requirements are high-quality genomic DNA and phenotypic information from a minimum of 500 patients with a confirmed diagnosis of IBD and of 500 population-matched healthy controls. Anyone interested in joining the consortium may contact enquiries@ibdgenetics.org.

Experimental Therapies: Study Results

Pipeline of IBD drugs

In a clinical update on inflammatory bowel disease (IBD) drugs in the developmental stage, Prof. William Sandborn (University of California San Diego, USA) said he expected a large majority of agents currently in phase 2 and phase 3 trials to reach the market. He claimed the drug armamentarium at the disposal of clinicians may double by 2025. All studies he mentioned were performed in patients with moderate-to-severe ulcerative colitis (UC) and Crohn's disease (CD).

In IBD, 2 integrin-targeting therapies are already available: natalizumab and vedolizumab, the latter being gut-selective. Investigational anti-integrin therapies are etrolizumab (RG7413), ontamalimab, abrilumab, AJM 300, and PTG-100. Etrolizumab selectively binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7. Positive results in a phase 2 study in UC patients [1] paved the way for a series of trials: 6 for patients with UC and 2 for patients with CD. Prof. Sandborn expected to receive phase 3 results of etrolizumab in the fall of 2020. Abrilumab, targeting the integrin α4β7, also showed promising results in UC after 8 weeks induction therapy in a phase 2b study [2]. Ontamalimab targets the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and showed promising results in UC [3].

Prof. Sandborn named 3 JAK inhibitors of which clinical data are available. TD-1473 is an orally administered topical pan-JAK inhibitor that is intestinally restricted, thus minimising systemic absorption. In an exploratory phase 1b study in UC, TD-1473 showed clinical response [4]; it is currently being tested in phase 2 and 3 trials. Two other JAK1 inhibitors, filgotinib and upadacitinib, showed encouraging results in phase 2 studies in CD [5,6].

Sphingosine-1-phosphate receptor 1 (S1P1)-modulators currently under investigation include fingolimod, ozanimod, etrasimod (APD334), and amiselimod. Ozanimod was tested in a preliminary trial in UC patients [7], but efficacy as well as safety requires further assessment in larger trials. In a phase 2 trial, etrasimod was effective in producing clinical and endoscopic improvements in UC patients [8].

Anti-IL-23 receptor monoclonal antibodies also hold promise for IBD treatment, Prof. Sandborn stated. He found phase 2 results of induction therapy with risankizumab in CD patients who had failed TNF inhibitors "the most encouraging endoscopic data I have ever seen in this population" [9]. Two other promising anti-IL-23-agents, brazikumab and mirikizumab, are in development for both UC and CD.

1. Vermeire S, et al. Lancet. 2014 ;384(9940):309-18.
2. Sandborn WJ, et al. Gastroenterology. 2019;156(4):946-957.e18.
3. Vermeire S, et al. Lancet. 2017;390(10090):135-44.
4. Sandborn WJ, et al. UEGW 2018, LB05.
5. Vermeire S, et al. Lancet. 2017;389(10066):266-75.
6. Sandborn WJ, et al. Gastroenterology. 2020 Feb 7. pii: S0016-5085(20)30167-0.
7. Sandborn WJ, et al. N Engl J Med. 2016;374(18):1754-62.
8. Sandborn WJ, et al. Gastroenterology. 2020;158(3):550–61.
9. Feagan BG, et al. Lancet. 2017;389(10080):1699-1709.

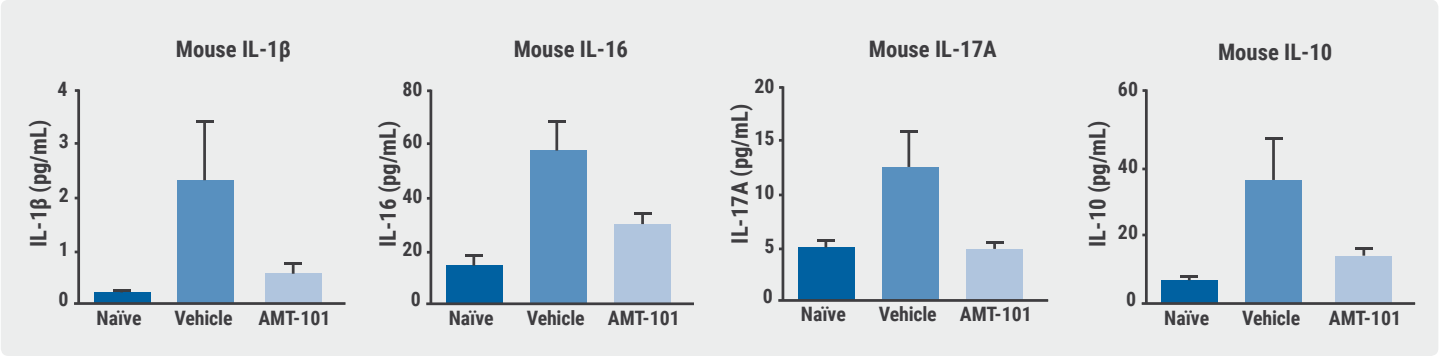
AMT-101: an oral human IL-10 fusion protein

A newly designed chimaera of human IL-10 genetically fused to a non-toxic and poorly immunogenic fragment of the cholix exotoxin, termed AMT-101, demonstrated efficacy in preclinical models of colitis and has advanced to the clinic. Its gastro-intestinal selectivity should lead to improved safety.

IL-10 is a central anti-inflammatory cytokine that can modulate many pro-inflammatory signals, but clinical application has been limited by dose-limiting systemic side effects. This led to the development of a new chimaera of human IL-10 termed AMT-101.

In mice, the oral gavage of AMT-101 blocked histological changes of colonic tissue associated with oxazolone-induced colitis [1]. AMT-101 curbed increases in serum levels of pro-inflammatory cytokines IL-1β, IL-6, and IL-17A, as well as IL-10 (see Figure). Cynomolgus monkeys dosed orally with AMT-101 showed much lower serum levels than after intravenous injection of AMT-101 [1]. First author Dr Randall Mrsny (Applied Molecular Transport, San Francisco, USA) said these studies provide strong evidence that AMT-101 can effectively reach the intestinal lamina propria to deliver biologically active IL-10 following transcytosis across the intestinal epithelium. The gut-selective nature of the responses suggests AMT-101 may avoid the systemic toxicity of IL-10.

Figure. Serum levels of IL-1β, IL-6, IL-17A, and IL-10 in naïve and in vehicle- and AMT-101-treated mice [1]



Dr Mrsny proposed that AMT-101 has potential as stand-alone as well as combination therapy. A phase 1a study of AMT-101 in healthy subjects has been completed; it is currently being evaluated in a phase 1b trial in patients with active ulcerative colitis. Dr Mrsny stressed that the use of AMT-101 needs not be limited to delivering IL-10: "It is capable of carrying any biological currently in the clinic".

1. Mrsny R, et al. ECCO-IBD 2020, OP39.

Phase 2 results of first-in-class TL1A inhibitor

In the phase 2a open-label TUSCANY study, PF-06480605 exhibited an acceptable safety and tolerability profile and statistically significant endoscopic improvement in participants with moderate-to-severe ulcerative colitis (UC) [1].

In UC, TNFα-like ligand 1A (TL1A), is upregulated at the site of active disease. PF-06480605 is a first-in-class fully human IgG1 monoclonal antibody targeting TL1A. In TUSCANY, participants received 7 doses of 500 mg intravenous PF-06480605 every 2 weeks and were then followed up for 14 weeks. Of the 50 participants who received PF-06480605, 42 completed the study.

At week 14, statistically significant endoscopic improvement (Mayo endoscopic subscore ≤1 without friability) was observed in 38.2% of participants; 24% achieved remission (total Mayo score ≤2, with no individual subscore >1) and 10% endoscopic remission (Mayo endoscopic subscore 0). In participants with endoscopic improvement, normalisation towards a non-inflamed transcriptome was demonstrated.

There were 109 treatment-emergent adverse events (AEs), 18 of which were deemed related to treatment. Aside from worsening UC, the most common treatment-emergent AE was arthralgia, which occurred in 6 participants, and was thought to be treatment-related in 1. Four treatment-emergent serious AEs were reported in 3 participants, 1 of which (alopecia) was thought to be treatment-related. There were no malignancies or deaths.

1. Danese S, et al. ECCO-IBD 2020, DOP72.

Open-label extension study of risankizumab: final results

In a final analysis of long-term treatment with open-label risankizumab in Crohn's disease, its safety profile remained consistent with previous data, with no new safety signals. Clinical remission as well as endoscopic remission was sustained [1].

Responders to risankizumab, an IL-23A antibody, in a phase 2 induction/maintenance study could enrol in an open-label extension (OLE). They received open-label 180 mg subcutaneous risankizumab every 8 weeks for up to 206 weeks. There were 65 Crohn's disease patients who enrolled in the OLE, with 4 patients re-induced; 60 patients (92%) had been previously treated with TNF antagonists. In the OLE, median exposure to risankizumab was 1,014 (range: 114–1,317) days.

At baseline of the current study, 47 patients (72%) had clinical remission, defined as Crohn's disease Activity Index (CDAI) <150. At baseline, 27 patients (42%) were in endoscopic remission, defined as Crohn's disease Endoscopic Index of Severity (CDEIS) ≤4 or CDEIS ≤2 for patients with isolated ileitis at baseline. Both clinical remission and endoscopic remission were sustained up to week 152 (see Table).

A third of the patients (n=21) prematurely discontinued risankizumab, including 6 (9%) who experienced an adverse event (AE). Sixty patients (92%) reported AEs; in 23 (35%) these

were serious. The most common AEs were nasopharyngitis (31%), gastroenteritis (23%), and fatigue (20%). Serious infections were reported in 6 patients (9%) and opportunistic infections in 3 patients (5%).

1. Ferrante M, et al. ECCO-IBD 2020, OP27.

Table. Clinical and endoscopic remission in patients receiving open-label risankizumab maintenance treatment [1]

Visits in OLE	Clinical remission, n/N		Endoscopic remission, n/N	
	NRI	Observed	NRI	Observed
Week 0	47/65 (72%)	47/65 (72%)	27/65 (42%)	27/63 (43%)
Week 8	48/65 (74%)	48/65 (74%)	-	-
Week 16	46/65 (71%)	46/64 (72%)	-	-
Week 48	46/65 (71%)	46/58 (79%)	35/65 (54%)	35/62 (56%)
Week 104	42/65 (65%)	42/49 (86%)	27/65 (42%)	27/43 (63%)
Week 152	23/65 (35%)	23/30 (77%)	23/65 (35%)	23/39 (59%)

NRI, non-responder imputation

Clinical remission after dose escalation of upadacitinib

Crohn's disease (CD) patients with non-response or loss of response to upadacitinib during the CELEST study gained clinical remission and endoscopic response with upadacitinib 12 mg twice daily or further escalation to 24 mg twice daily. There were no new safety signals for either dose of this oral selective JAK1 inhibitor.

CELEST was a phase 2 study of adults with moderate-to-severe CD refractory to immunosuppressants/biologics [1]. Patients were randomised to placebo or upadacitinib 3, 6, 12, or 24 mg twice daily, or 24 mg once daily for 16 weeks (n=220), followed by 3, 6, or 12 mg twice daily, or 24 mg once daily in a double-blind maintenance period of 36 weeks (n=180). Patients with inadequate response (n=60) received open-label upadacitinib 12 mg twice daily, with further escalation to 24 mg twice daily possible if an adequate response was not achieved by at least 4 weeks of open-label treatment.

After 16 weeks of open-label treatment, 25 (42%) had clinical response; 27 patients (45%) required escalation to upadacitinib 24 mg twice daily. At week 52, 15% and 10% of patients in the 12 mg group achieved clinical remission and endoscopic response, respectively. In the 24 mg group, these percentages were 39% and 41%. Three patients had a serious infection (2 receiving 12 mg). There were no malignancies, cardiovascular events, thromboembolic events, intestinal perforations, tuberculosis, or deaths in the dose-escalated groups.

An analysis of the phase 2b U-ACHIEVE study found that upadacitinib modulates expression of serum pro-inflammatory mediators found in pathways associated with the pathogenesis of ulcerative colitis [2]. Upadacitinib increased expression of mediators that promoted haematopoiesis, neuroprotection, and mucosal repair. Clinical improvements in ulcerative colitis were found to correlate with changes in biomarkers associated with reduced inflammation and improved haematopoiesis, mucosal repair, and neuroprotection/neurodegeneration.

1. Sandborn W, et al. ECCO-IBD 2020, DOP79.
2. Vermeire S, et al. ECCO-IBD 2020, DOP17.

Possible new treatment targets in IBD

New treatment targets that have been tested preclinically or clinically are: highly selective small-molecule oral inhibitors of integrin α4β7, a CEACAM5 small peptide, the selective histone deacetylase (HDAC)6 inhibitor CKD-506, and a potent SIRT2-specific inhibitor, thiomyristoyl.

Integrins help facilitate immune cell trafficking and are an important receptor family for therapeutic intervention. The α4β7 integrin is an already clinically validated target for the treatment of inflammatory bowel disease (IBD): vedolizumab blocks the interactions between α4β7-expressing lymphocytes and its ligand mucosal addressin cell adhesion molecule-1 (MadCAM-1). In a study to develop and characterise orally bioavailable small-molecule inhibitors of the α4β7 integrin, a number of potent, selective, α4β7 integrin inhibitors were discovered that demonstrate on-target, mechanistic efficacy in 2 animal models of IBD [1]. The lead compound had favourable drug metabolism and pharmacokinetic properties, good oral bioavailability, and probably sufficient exposure in humans to effectively block α4β7-expressing immune cells. The authors therefore claimed this result could lead to an effective and safe monotherapy for IBD, which may also be combined with other IBD drugs.

Another study highlighted a new approach for modulating inflammation in Crohn's disease (CD) by means of CEACAM5 small peptide [2]. Previously, a small region in CEACAM5 was identified that is able to restore the suppressive activity of CD8+ Treg cells in CD. In the new study, CEACAM5 small peptide activated CD8+ T cells from CD patients and significantly suppressed CD4+ T-cell proliferation [2]. The strongest suppression of proliferation was induced by a new small peptide from the overlapping peptide library containing

N71. Peripheral CD8+ T cells increased IL-10 production upon stimulation with the CEACAM5 peptide.

CKD-506 is a selective inhibitor of HDAC6, a stress-inducible gene that is highly expressed in IBD. Molecular mechanisms of CKD-506 were identified [3]. CKD-506 was found to exert anti-inflammatory and anti-colitis effects through regulation of the NF-κB and AP-1 signalling pathway. Therefore, CKD-506 may provide beneficial effects in IBD patients.

Thiomyristoyl is a potent specific inhibitor of the HDAC SIRT2. Thiomyristoyl has shown extensive anticancer activity. A study of its anti-inflammatory properties revealed that thiomyristoyl ameliorates experimental colitis by blocking the differentiation of Th17 cells, which may be associated with the STAT3/IL-6 signal pathway [4]. The authors concluded SIRT2 may represent a potential target for IBD treatment.

1. Wong J, et al. ECCO-IBD 2020, DOP64.
2. Roda G, et al. ECCO-IBD 2020, DOP66.
3. Shin J, et al. ECCO-IBD 2020, DOP67.
4. Xu Y, et al. ECCO-IBD 2020, DOP68.

Short- and Long-Term Treatment Results

Infliximab discontinuation increases relapse risk

In a randomised prospective trial, discontinuation of maintenance infliximab increased the risk of relapse of ulcerative colitis (UC) [1]. Retreatment was found to be effective. Endoscopic normalisation did not guarantee successful withdrawal.

UC patients treated with infliximab who were in clinical remission were enrolled from 23 specialised centres in Japan in this first-ever prospective, multicentre, randomised controlled trial to evaluate the effects of discontinuing a TNF inhibitor. Participants had to be in clinical remission for >6 months, be steroid-free, and have a Mayo endoscopic subscore (MES) of 0 or 1. They were randomised 1:1 to continuation or discontinuation of infliximab. The primary endpoint was remission rate after 48 weeks in a full analysis set. A total of 92 patients were included in the full analysis set; 46 in each group.

After 48 weeks, remission was maintained by 37 of 46 patients (80.4%) who had continued infliximab (95% CI 66.1–90.6), versus 25 of 46 patients (54.3%) who had not (95% CI 39.0–69.1; P=0.008). C-reactive protein and Nancy histological index were associated with remission at week 48 (P=0.039 and P=0.019, respectively). Not predictive of remission were infliximab concentration or treatment duration, use of concomitant immunomodulators, and a MES of 0 at randomisation. Retreatment in patients who had discontinued infliximab was well-tolerated and led to renewed remission in 8 of 12 patients (66.7%) after 8 weeks.

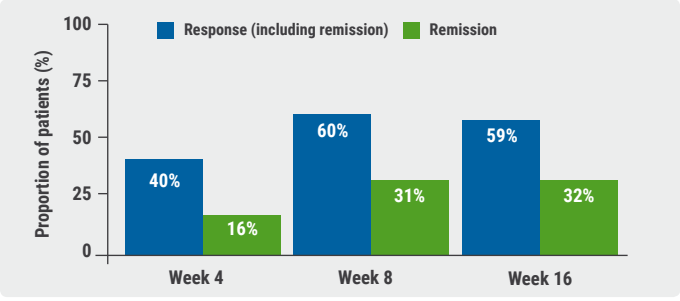
1. Kobayashi T, et al. ECCO-IBD 2020, DOP39.

Tofacitinib 'real-world' effectiveness in active UC

Tofacitinib is relatively effective in ulcerative colitis (UC) patients in real practice, even in a highly refractory cohort of patients from the prospectively maintained ENEIDA registry [1]. Only 12% of patients not in remission at week 8 reached remission at week 16.

Clinical activity and effectiveness were defined in terms of partial Mayo score (PMS). Included were 113 UC patients who were exposed to tofacitinib for a median of 44 weeks. After 8 weeks, response and remission rates were 60% and 31%, respectively; these rates were still similar at week 16 (see Figure). Higher PMS at week 4 (OR 0.2; 95% CI 0.1–0.4) was associated with a reduced odds of achieving remission after 8 weeks. Higher PMS at week 4 (OR 0.5; 95% CI 0.3–0.7) and higher PMS at week 8 (OR 0.2; 95% CI 0.1–0.5) were associated with a lower chance of remission after 16 weeks. Of patients not in remission at week 4 and week 8, 20% and 12% achieved remission after 16 weeks. Noteworthy, 65% of patients in remission at week 8 relapsed within the next year.

Figure. Short-term effectiveness of tofacitinib in ulcerative colitis (last-observation-carried-forward method) [1]



Primary failure was the main reason for a total of 45 patients (40%) to discontinue tofacitinib over time. Only PMS at week 8 was associated with discontinuation (HR 1.5; 95% CI 1.3–1.6). Eighteen patients had adverse events, of which 4 were hypercholesterolaemia. No thromboembolic events were reported.

Early 'real-world' experience with tofacitinib in 4 UK tertiary centres resulted in similar efficacy and safety outcomes as had been reported in the pivotal OCTAVE clinical trials [2]. Response and remission rates were 73% (81/111) and 56% (62/111) respectively at week 8, and 48% (39/82) and 39% (32/82) respectively at week 26. Steroid-free remission was reached by 47% (52/111) and 37% (30/82) at week 8 and 26. There were 6 serious infections.

1. Chaparro M, et al. ECCO-IBD 2020, OP29.
2. Chee D, et al. ECCO-IBD 2020, DOP69.

Ustekinumab in CD: a T2T trial

Clinical and endoscopic results of the STARDUST trial of ustekinumab in patients with moderate-to-severe Crohn's disease (CD) showed two-thirds of patients achieved clinical remission after 16 weeks of ustekinumab induction. Of responders then randomised to the treat-to-target (T2T) arm, 37% showed endoscopic response after another 16 weeks [1].

STARDUST is an ongoing phase 3b randomised strategy trial of ustekinumab in CD. "This is the first T2T trial in CD patients using endoscopy at week 16 as a decision point for dose adjustment", explained Prof. Laurent Peyrin-Biroulet (CHRU de Nancy, France). Eligible for enrolment were CD patients who failed conventional therapy and at most 1 biologic. At baseline, patients received intravenous ustekinumab of ~6 mg/kg induction and, at week 8, subcutaneous ustekinumab 90 mg. After 16 weeks, patients with a Clinical Disease Activity Index (CDAI) reduction of ≥70 points were randomised to T2T or standard of care.

The intention-to-treat (ITT) full set included 500 patients. After 16 weeks, 79.4% of patients had a clinical response; 66.6% were in clinical remission. About half of the patients showed ≥50% improvement in faecal calprotectin (FCP) and C-reactive protein (CRP) levels, which normalised in about one third of patients. Of patients with a response after 16 weeks, 84% were in clinical remission. There were statistically significant changes from baseline in CDAI, FCP, and CRP at week 8, and in Inflammatory Bowel Disease Questionnaire (IBDQ) scores at week 16. Of patients in the T2T group (n=220), 36.8% achieved endoscopic response after 16 weeks, while 11.4% achieved remission. Endoscopic response was numerically better for colonic versus ileal disease. Prof. Peyrin-Biroulet added that no new safety signals were reported.

1. Danese S, et al. ECCO-IBD 2020, DOP13.

Subcutaneous ustekinumab as maintenance therapy in UC

The efficacy of ustekinumab through 92 weeks in patients with moderate-to-severe ulcerative colitis (UC) who had been randomised in the UNIFI maintenance study was presented [1]. This study evaluated subcutaneous ustekinumab through 1 year in responders to intravenous ustekinumab induction. Patients who completed the maintenance study could enter a long-term extension (LTE) through 220 weeks.

During the LTE, participants were eligible to receive dose adjustment (every 12 weeks [Q12W] to every 8 weeks [Q8W] or sham dose adjustment of Q8W to Q8W) starting at week 56. Symptomatic remission (stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0) and partial Mayo remission (partial Mayo score ≤2) were evaluated through week 92. When dose adjustment was considered to be part of the treatment experience (i.e., not a treatment failure), ustekinumab efficacy was maintained through 2 years of treatment. Of patients randomised to Q12W and Q8W, 66.1 % and 67.0% respectively, were in symptomatic and partial Mayo remission after 2 years. There were no clinically meaningful differences between the Q12W and Q8W dose groups. When dose adjustment was considered to be a treatment failure in the analysis, 53.2% and 54.0% of patients were in symptomatic and partial Mayo remission, respectively. There were no new safety signals in the second year.

A subanalysis of the UNIFI maintenance study looked at health-related quality of life through week 92 in patients who continued ustekinumab maintenance therapy in the LTE [2]. The majority of patients who received ustekinumab in the LTE maintained the improvements in Inflammatory Bowel Disease Questionnaire (IBDQ) and Short-Form Health Survey (SF-36) that were achieved after intravenous induction. Of 284 patients receiving ustekinumab, 158 (55.6%) were in IBDQ remission at week 92; of 169 patients who were in IBDQ remission at maintenance baseline, 114 (67.5%) were in IBDQ remission at week 92. In 179 of 284 patients (63.0%) a ≥16-point improvement in IBDQ score was observed.

1. Panaccione R, et al. ECCO-IBD 2020, DOP12.
2. Sandborn WJ, et al. ECCO-IBD 2020, DOP56.

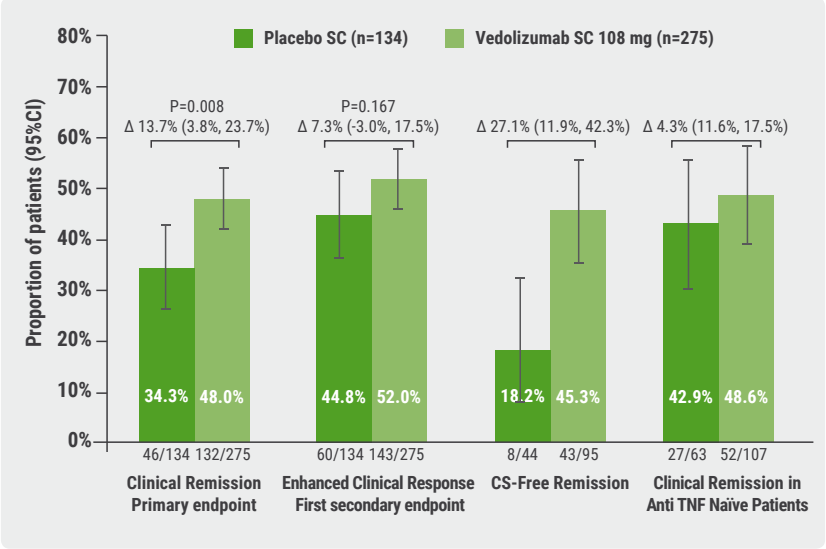
Subcutaneous vedolizumab maintenance therapy in CD

The first phase 3 study results of subcutaneous vedolizumab maintenance treatment in moderate-to-severe Crohn's disease (CD) showed that among vedolizumab induction responders, significantly more patients on vedolizumab achieved clinical remission after 1 year than on placebo [1].

Prof. Séverine Vermeire (University Hospital Leuven, Belgium) presented the results of the VISIBLE 2 study of subcutaneous vedolizumab as maintenance treatment CD. The 644 participants received intravenous vedolizumab 300 mg at weeks 0 and 2 as induction therapy. At week 6, the 412 clinical responders were then randomised to receive 108 mg subcutaneous vedolizumab (n=275) or placebo (n=134) every 2 weeks for up to 52 weeks. The primary endpoint was clinical remission at week 52, defined as a Crohn's disease Activity Index (CDAI) score ≤150.

The primary endpoint was achieved by 48.0% of patients on subcutaneous vedolizumab versus 34.3% on placebo (P=0.008). Enhanced clinical response (decrease of ≥100 in CDAI score) was not significantly different: 52.0% versus 44.8% (P=0.167; see Figure). Prof. Vermeire stated that "the high placebo response may be explained by the carry-over effect of induction therapy". Among patients on concomitant corticosteroids at baseline (n=95 and n=44 in the respective treatment groups), 45.3% versus 18.2% achieved corticosteroid-free clinical remission. Of anti-TNF-naïve patients, 48.6% and 42.9% achieved clinical remission.

Figure. Primary and secondary endpoints of VISIBLE 2 (full analysis set) [1]



SC, subcutaneous; CS, corticosteroid

Less than 3% of patients treated with subcutaneous vedolizumab reported injection-site reactions. Serious infections, malignancy, and liver injury were seen in ≤5% in both arms. Numerically, serious infections were lower in the treatment group (n=4) versus placebo (n=6). Anti-vedolizumab antibodies were detected in 7 (2.5%) treated patients; 4 of 7 developed neutralising antibodies. There were no new safety signals.

1. Vermeire S, et al. ECCO-IBD 2020, OP23.

Vedolizumab treatment persistence and safety

In an extended access program (XAP), patient persistence on vedolizumab every 8 weeks (Q8W) was high in the first 2 years after reduction of dosing frequency [1]. Overall, there were low rates of dose escalation (to every 4 weeks [Q4W]) and ulcerative colitis (UC) or Crohn's disease (CD) disease relapse. The safety profile was consistent with previous reports.

The prospective, open-label vedolizumab XAP study enrolled 311 patients (142 UC, 169 CD) who had benefitted from vedolizumab in the GEMINI long-term safety study. They could remain on vedolizumab 300 mg intravenous Q4W if medically indicated. However, the large majority of UC and CD patients (93.0% and 84.6%) reduced dosing frequency at XAP start from Q4W to Q8W; 87.3% and 77.5% were still on Q8W after 2 years. At baseline, 93.0% and 88.2% of UC and CD patients were in corticosteroid-free remission.

Of patients who initiated Q8W dosing at enrolment in the XAP, 95% had no relapse for ≥6 months (97.0% UC, 93.7% CD). Only 7.3% of patients required dose escalation to Q4W. Time to dose escalation and to relapse were similar in UC and CD patients. Adverse events related to vedolizumab were infrequent; no new or serious events attributed to this treatment were reported.

In a binational, multicentre, retrospective case-control study, vedolizumab was found to have similar efficacy rates in young (n=140) vs elderly (n=144) patients with UC or CD [2]. The respective average age was 29.6 and 70.2 years. An increased risk of overall infections in the elderly cohort was noted, but it is unclear whether this was related to vedolizumab treatment.

1. Danese S, et al. ECCO-IBD 2020, DOP60.
2. Cohen NA, et al. ECCO-IBD 2020, DOP57.

Specific Therapeutic Strategies

On the cutting edge of pathology and surgery

There is no place for the pathologist in the operating room or for the surgeon at the microscope, argued pathologist Prof. Paula Borralho Nunes (University of Lissabon, Portugal) and surgeon Prof. Antonino Spinelli (Humanitas Research Hospital, Italy) at a tandem talk on pathology-guided surgery. However, the diagnosis and correct management of inflammatory bowel disease (IBD) demands multidisciplinary teamwork, and the 2 speakers agreed that the surgeon and pathologist should meet before (especially to discuss pouch surgery and dysplasia), during (in case of suspicion for malignancies), and after surgery.

Prof. Borralho Nunes and Prof. Spinelli discussed how the pathologist might support the surgeon in order to reshape surgery for IBD and achieve better results.

First, pathology plays a major part in the diagnostic process, and a correct diagnosis has a major impact on the choice between surgical options. Additionally, the analysis of histological features can predict post-operative recurrence. So, for example, pathology is crucial in the selection of pouch candidates. A meta-analysis of 17 studies revealed that patients with indeterminate colitis (IC) –or rather IBD unclassified (IBDU)– had a higher anastomotic leak rate and a higher overall complication rate than patients with ulcerative colitis (UC) [1]. In IC patients, subtotal colectomy may therefore generally be a better option. This allows for pathological reassessment, as well as discussion within a multi-disciplinary team and with the patient about options and risks, before making a final surgical decision.

Another subject on the 'cutting edge' of pathology and surgery is the evaluation of disease activity at resection margin in Crohn's Disease (CD). Several studies were highlighted to illustrate the importance.

- The presence of involved histological margins has been associated with a higher risk of recurrence [2].
- Patients with transmural lesions at the ileal margin were shown to have an increased risk of post-operative recurrence versus patients without these lesions (75% vs 46%), which is why histologic features of the ileal margin should be considered when discussing post-operative therapy [3].
- Submucosal lymphocytic plexitis in the proximal surgical margin has been significantly associated with a higher risk of endoscopic recurrence of CD after ileocolonic resection [4].
- Increased enteric glial cells in the proximal margin of resection have been associated with postoperative recurrence of CD [5].
- Granulomatous CD has been associated with a higher risk as well as a shorter time to recurrence and reoperation [6].

Prof. Borralho Nunes and Prof. Spinelli ended their talk by emphasising the need to standardise reporting on IBD surgical specimens. Summarised reports following a prespecified scheme will facilitate completeness and communication. Publication of the ECCO Topical Review 'Optimising reporting on surgery, endoscopy and histopathology' is scheduled for late 2020.

1. Emile SH, et al. J Crohns Colitis. 2020 Jan 8. pii: jjaa002.
2. Ryan JM, et al. Dis Colon Rectum. 2019 Jul;62(7):882-892.
3. Hammoudi N, et al. Clin Gastroenterol Hepatol. 2020;18(1):141-9.
4. Lemmens B, et al. J Crohns Colitis. 2017;11(2):212-20.
5. Li Y, et al. J Gastroenterol Hepatol. 2018;33(3):638-44.
6. Simillis C, et al. Dis Colon Rectum. 2010;53(2):177-85.

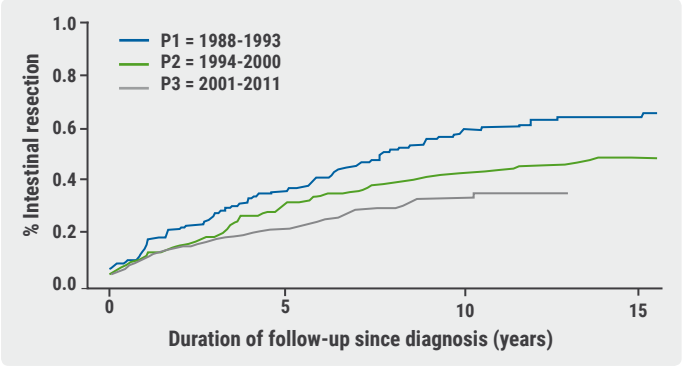
Impact of strategies on intestinal resection rate

A population-based cohort study in paediatric-onset inflammatory bowel disease (IBD) patients looked at the impact of therapeutic strategies on intestinal resection rate over a period of 24 years [1]. In parallel with the increased use of immunosuppressants and anti-TNF agents, resection rate within 5 years after diagnosis decreased in paediatric Crohn's disease (CD).

Children with IBD of 16 years and younger between 1988 and 2011 were drawn from a prospective French study and were retrospectively followed until 2013. Three diagnostic periods were distinguished: 1988–1993 (P1), 1994–2000 (P2), and 2001–2011 (P3). Risks for intestinal resection, hospitalisation, and complicated CD behaviour (stricturing or penetrating) were assessed and compared 5 years after diagnosis. A total of 800 patients with CD and 261 with ulcerative colitis (UC) were followed up for a median of 8.9 years. Exactly half of them (n=531) were boys; median age at diagnosis was 14.3 years.

Risk for intestinal resection significantly declined in CD from 35% (P1) to 20% (P3), at 5 years (P<0.05; see Figure).

Figure. Intestinal resection in CD patients according to the period of diagnosis [1]



Colectomy risk in UC did not change significantly (P1: 14%, P2: 19%, P3: 9%; P=0.08). Other results:

- In CD, immunosuppressant exposure increased from 32% (P1) to 75% (P3), anti-TNF exposure increased from 0% (P1) to 51% (P3) at 5 years.
- In UC, immunosuppressant and anti-TNF exposure increased from 9% (P1) to 65% (P3) and from 0% (P1) to 40% (P3), respectively.
- Exposure to corticosteroids remained the same (P1: 10%, P2: 10%, P3: 8%; P=0.54).
- Risk for IBD-flare-related hospitalisation at 5 years remained similar in CD (P1: 43%, P2: 45%, P3: 43%; P=0.60) as well as in UC (P1: 31%, P2: 46%, P3: 52%; P=0.10).
- Progression to a complicated behaviour in CD did not change (P1: 31%, P2: 33%, P3: 25%; P=0.20).

1. Ley D, et al. ECCO-IBD 2020, OP02.

Early ileocaecal resection in CD patients failing conventional treatment

In the LIR!C trial, laparoscopic ileocaecal resection in Crohn's disease (CD) patients not responding to conventional treatment was at least as good as anti-TNF in terms of quality of life and was cost-saving [1]. Long-awaited long-term follow-up data support early surgery in these patients [2].

In the original LIR!C trial, 73 patients with limited, non-stricturing, ileocaecal CD who had failed on conventional therapy were allocated to have resection and 70 to receive infliximab [1]. At 12 months, the mean Inflammatory Bowel Disease Questionnaire (IBDQ) score was 178.1 and 172.0 in the respective groups (P=0.25).

Long-term follow-up data were presented by Dr Toer Stevens (Amsterdam UMC, the Netherlands). In the resection group, 18 (26%) patients started anti-TNF treatment, none required a second resection, and 29 (42%) did not require additional CD-related treatment [2]. In the infliximab group, 31 (48%) patients moved on to a CD-related resection. In both groups, around 60% of patients required additional treatment at some point during follow-up. Duration of treatment effect was similar: median time without additional treatment was 33 months (95% CI 15.1–50.9) and 34 months (95% CI 0–69.3) in the resection and infliximab group, respectively (P=0.521). In both groups, prophylactic immunomodulators decreased the risk of additional treatment. Dr Stevens concluded: "These data support early laparoscopic ileocaecal resection in non-stricturing ileocaecal CD patients failing conventional treatment."

1. Ponsioen CY, et al. Lancet Gastroenterol Hepatol. 2017;2(11):785-792.
2. Stevens T, et al. ECCO-IBD 2020, OP03.

Biologics before surgery in IBD do not elevate infection risk

Exposure to biologics within 60 days of surgery for inflammatory bowel disease (IBD) was not associated with postoperative infection risk in a large retrospective cohort. In a univariate analysis, biologics before proctectomy were associated with an increased risk of anastomotic leak [1].

The results were presented by colorectal surgeon Dr Stefan Holubar (Cleveland Clinic, USA). "A well-validated methodology was used", he stressed. "Also, vigorous adjustment was performed for disease- and surgery-specific covariates, most notably diagnosis, chronic steroid use, immunomodulator (IMM) use, ostomy construction, anaemia, malnutrition, operative length, and emergency surgery." The primary endpoint was any infectious complication and the secondary endpoint was any surgical site infection. Of 1,562 included patients, 730 (47%) had been exposed to biologics before surgery. There was a higher prevalence of preoperative weight loss, lower albumin, systemic sepsis, IMM and steroid use, and of Crohn's disease (all P<0.001) in the biologics group. In this group, patients were also more likely to receive a new ostomy and to have a colectomy, while fewer had elective surgery (all P<0.001).

Biologics were not associated with any postoperative infectious complication (OR 0.88; 95% CI 0.54–1.42) or surgical site infection (OR 0.77; 95% CI 0.46–1.28). "This is likely due to judicious use of ileostomies," Dr Holubar stated. Crohn's disease was associated with any infectious complications (OR 2.11; 95% CI 1.12–4.0, P=0.02). There was also a strong signal of an association between biologics and an increased rate of anastomotic leak after proctectomy (6.7% vs 1.9%, P=0.02).

1. Holubar H, et al. ECCO-IBD 2020, OP25.

Top-down infliximab superior to step-up in children with CD

Usually, a step-up treatment strategy is applied for infliximab in paediatric Crohn's disease (CD) patients. In a first-ever direct comparison however, a top-down strategy was superior to step-up in achieving sustained clinical remission [1]. The authors therefore advise to start infliximab directly after diagnosis in moderate-to-severe paediatric CD.

Study presenter Myrthe Jongsma (Erasmus MC, the Netherlands) received an award for best investigator-initiated abstract at the ECCO-IBD 2020 meeting. Eligible patients in this study were aged 3–17 years and had new-onset, untreated disease with a weighted paediatric CD activity index (wPCDAI) >40. Top-down treatment consisted of 5 infliximab (CT-P13) infusions of 5 mg/kg (in week 0, 2, 6, 14, and 22) combined with azathioprine. Step-up treatment comprised exclusive enteral nutrition or oral prednisolone as induction, plus azathioprine as maintenance treatment. The primary endpoint was sustained clinical remission (wPCDAI <12.5) at week 52 without additional therapy or surgery. A total of 97 patients were randomised to top-down (n=49) or step-up (n=48).

After 52 weeks, significantly more patients in the top-down group were in clinical remission (44%) than in the step-up group (17%; P=0.004). Infliximab was (re)started after induction therapy in 39% of top-down versus 62% of step-up patients (P=0.019). After 10 weeks, top-down- compared with step-up-treated patients had higher clinical remission rates (61% vs 39%; P=0.033), higher endoscopic remission rates (59% vs 17%; P=0.001), and more frequent faecal calprotectin levels of <250 µg/g (53% vs 26%; P=0.027).

1. Jongsma M, et al. ECCO-IBD 2020, OP38.

High versus standard adalimumab in active UC

Higher maintenance doses of adalimumab resulted in more clinical responders after 1 year than standard doses. However, the difference did not reach statistical significance [1].

Prof. Jean-Frederic Colombel (Icahn School of Medicine at Mount Sinai, USA) explained that SERENE-UC was a phase 3, double-blind, randomised study evaluating higher versus standard adalimumab dosing regimens in 852 adult patients with moderate-to-severe ulcerative colitis (UC). After 8 weeks, responders (n=757) were re-randomised to either adalimumab 40 mg every week (40 EW); adalimumab 40 mg every other week (40 EOW); or exploratory adalimumab 40 mg with therapeutic drug monitoring (TDM) regimens. The primary efficacy endpoint was clinical remission, defined as a full Mayo score ≤2 with no subscore >1 at week 52. A total of 371 patients were included in the intention-to-treat (ITT)-group: 152, 145, and 74 in the respective treatment arms. Overall mean adalimumab exposure was 252.2 days.

Clinical remission at week 52 was reached by 39.5%, 29.0%, and 36.5% of patients in the respective treatment arms; see Table for all efficacy outcomes. Prof. Colombel concluded: "In patients receiving adalimumab 40 EW, clinical remission was 10.5% higher among week 8 responders compared with 40 EOW maintenance regimens, but this difference was not statistically significant. However, the integrated data of the main study and a small study performed in Japan (n=89) demonstrated significantly greater clinical remission rates at week 52 with 40 EW versus 40 EOW, with a difference of 11.1% (P=0.045). The safety of 40 EW and 40 EOW was similar; there were no new safety signals."

1. Colombel JF, et al. ECCO-IBD 2020, OP01.

Table. Efficacy endpoints among week 8 responders of SERENE-UC at week 52 [1]

	Adalimumab 40 mg EW, n/N	Adalimumab 40 mg EOW, n/N	Adalimumab TDM regimen, n/N
Primary endpoint			
Clinical remission	60/152 (39.5%)	42/145 (23.9%)	27/74 (36.5%)
Treatment difference	10.5% (95% CI -0.8 to 20.6); P=0.069		
Secondary efficacy endpoints			
Endoscopic improvement	78/152 (51.3)	60/145 (41.4%)	34/74 (45.9%)
Steroid-free for ≥90 days*	71/95 (74.7%)	49/92 (53.3%)	34/47 (72.3%)
Steroid-free for ≥90 days and in clinical remission*	37/95 (38.9%)	25/92 (27.2%)	19/47 (40.4%)
IBDQ response	101/152 (66.4%)	9/26 (34.6%)	10/16 (62.5%)

*of week 8 responders taking steroids at baseline; EW, every week; EOW, every other week; TDM, therapeutic drug monitoring; IBDQ, Inflammatory Bowel Disease Questionnaire

Head-to-Head Comparison of Treatments

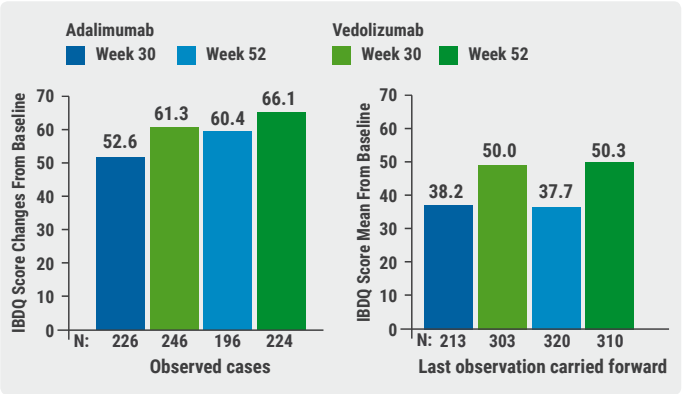
Effects of vedolizumab versus adalimumab on QoL

The effects of intravenous vedolizumab versus adalimumab on quality of life (QoL) were compared in a subanalysis of the VARSITY trial. More ulcerative colitis (UC) patients treated with vedolizumab than with adalimumab achieved clinically meaningful improvement and clinical remission, based on the Inflammatory Bowel Disease Questionnaire (IBDQ) scores [1].

VARSITY was the first head-to-head trial comparing the efficacy and safety of biologics in patients with moderately to severely active UC, and was one of the highlights of the 2019 edition of the ECCO-IBD meeting [2,3]. To assess QoL, the IBDQ was used. Clinically meaningful IBDQ improvement was defined as an increase in total score of ≥16 points from baseline to week 52; IBDQ remission was a total score of >170 points at week 52.

Results showed a clinically meaningful IBDQ improvement at week 52 in 199/383 patients (52.0%) versus 163/386 (42%) in the vedolizumab and adalimumab group, respectively (treatment difference 9.7%). IBDQ remission was achieved by 192 (50%) and 156 (40%) patients, respectively (treatment difference 9.6%). Mean changes in IBDQ total score from baseline for observed cases favoured vedolizumab over adalimumab (see Figure). IBDQ subscores showed similar favourable trends for vedolizumab. Reduced inflammation, as indicated by improvements in C-reactive protein (CRP) and faecal calprotectin (FCP), was consistent with improvements in QoL.

Figure. IBDQ total score changes from baseline at weeks 30 and 52 (full analysis set) [1]



Using efficacy data of the VARSITY trial, another study compared the cost-effectiveness of vedolizumab and adalimumab [4]. The clinical foundation of this model is predicated primarily on head-to-head evidence from phase 3 trials. Modelled outcomes indicated that UC patients are likely to achieve better clinical outcomes, as vedolizumab was associated with higher induction response (52.9% vs 45.1%) and remission rates (22.0% vs 14.4%). Also, based on US payer costings, lower direct medical costs are associated with vedolizumab (USD $90,673) than with adalimumab (USD $137,007), though this may not be applicable to other countries.

1. Loftus EV, et al. ECCO-IBD 2020, DOP24.
2. Schreiber S, et al. ECCO-IBD 2019, OP34.
3. Sands BE, et al. N Engl J Med. 2019 Sep 26;381(13):1215-1226.
4. Schultz R, et al. ECCO-IBD 2020, P607.

Vedolizumab and anti-TNF therapies: a real-world comparison

In a real-world comparison of vedolizumab and anti-TNF therapies in biologic-naïve ulcerative colitis (UC) patients, vedolizumab was associated with higher persistence, lower likelihood of exacerbations and a better safety profile [1]. However, sample size limitations necessitate further study.

The EVOLVE study is one of the first to compare a biological with anti-TNF as early treatment of UC. It was a real-world, multi-country, retrospective chart review study in Canada, Greece, and the USA. The clinical effectiveness and safety of vedolizumab or an anti-TNF (adalimumab, infliximab, or golimumab) as a first-line biologic initiated within 2 years after diagnosis were assessed. A total of 176 UC patients from 37 sites were included in the analysis: 86 using vedolizumab and 90 using anti-TNF. The mean age in both groups was 41.4 and 36.8 years, respectively. The proportion of men was 58.1% and 56.7%, respectively.

At 12 months, 72.9% and 58.1% still used vedolizumab and anti-TNF respectively (P=0.03). There were no differences in clinical response, clinical remission, or mucosal healing. However, vedolizumab users had a significantly lower risk of UC exacerbations (HR 0.47; 95% CI 0.32–0.69) and serious adverse events (HR 0.37; 95% CI: 0.19–0.72). The authors concluded that, based on these findings, early treatment with vedolizumab may improve long-term clinical outcomes.

1. Mantzaris G, et al. ECCO-IBD 2020, DOP55.

Vedolizumab, adalimumab, and golimumab compared

In real-life Italian data comparing clinical effectiveness of vedolizumab, adalimumab, and golimumab in ulcerative colitis (UC) patients, vedolizumab was superior to both anti-TNF agents in achieving clinical benefit at 52 weeks, and also in terms of treatment persistence [1].

The clinical endpoints were steroid-free clinical remission (partial Mayo score <2 without steroid use) and clinical response (reduction of the partial Mayo score ≥2 points with a concomitant decrease of steroid dosage compared with baseline). A total of 463 patients were included (vedolizumab, n=187; adalimumab, n=168; golimumab, n=108). Median follow-up was 47.6 weeks.

After 8 weeks, a clinical benefit was achieved in 70.6%, 68.5%, and 67.6% of patients in the vedolizumab, adalimumab, and golimumab group, respectively. After 52 weeks, vedolizumab showed better rates of clinical benefit than adalimumab (71.6% vs 47.5; P<0.001) and golimumab (71.6% vs 40.2%; P<0.001); there was no significant difference between adalimumab and golimumab. In the vedolizumab group, the risk of treatment discontinuation was lower than in the adalimumab group (HR 0.42; P<0.001) and golimumab (HR 0.30; P<0.001). Post-treatment mucosal healing rate was non-significantly better in the vedolizumab group (48.1%) versus the adalimumab and golimumab groups (38.0% and 34.6%, respectively).

Another Italian real-life study also compared efficacy of vedolizumab, adalimumab, and golimumab, but they added infliximab originator (IFX-O) as well as infliximab biosimilar (CTP-13) [2]. The primary endpoint was relapse-free, optimisation-free, steroid-free remission at 1 year, defined as Mayo partial score ≤2, with bleeding subscore 0, no relapse after first clinical remission and no optimisation with dose intensification or steroid courses. A total of 492 patients were included.

Overall, 65% achieved clinical remission during follow-up, with infliximab originator performing better than golimumab and vedolizumab. Relapse rate was lowest in the vedolizumab group. Based on the strict definition of clinical remission, all biologics appeared equally effective at 1 year, except when comparing golimumab with infliximab originator. Infliximab originator also appeared more effective in other clinical outcomes (see Table). CTP-13 had more frequent adverse events (mainly infusion reactions) than the other drugs. The authors claimed that infliximab originator should be used as the reference drug in head-to-head, controlled, comparison trials of biologicals in UC.

1. Macaluso FS, et al. ECCO-IBD 2020, P690.
2. Cassinotti A, et al. ECCO-IBD 2020, P566.

Table. Primary and secondary outcomes [2]

Endpoint	Infliximab originator (n=76)	Adalimumab (n=90)	CTP-13 (n=105)	Golimumab (n=79)	Vedolizumab (n=142)
First clinical remission	79%	71%	62%	57%	62%
Relapse rate	30%	29%	20%	24%	20%
1-year clinical remission	64%	51%	50%	37%	42%
1-year relapse rate, steroid-free remission	41%	32%	38%	28%	37%
1-year persistence on treatment	72%	54%	55%	42%	63%
1-year endoscopic remission	16%	18%	11%	13%	11%
Treatment failure (efficacy)	20%	44%	33%	52%	36%
Treatment failure (safety)	9%	2%	13%	4%	1%
Adverse events	18%	10%	28%	19%	11%

Vedolizumab versus ustekinumab

In 2 comparative studies, ustekinumab was found to be more effective than vedolizumab in patients with Crohn's disease (CD) refractory to anti-TNF. Safety outcomes were comparable.

A French head-to-head study included 239 patients, of whom 107 received ustekinumab and 132 vedolizumab [1]. After propensity scoring, there was no difference between the groups. After 48 weeks, the clinical remission rate was higher in the ustekinumab versus the vedolizumab group (54.4% vs 38.3%; OR 1.92; 95% CI 1.09–3.39). Other results after 48 weeks:

- Corticosteroid-free remission was numerically higher in the ustekinumab group (44.7% vs 34.0%; OR 1.57; 95% CI 0.88–2.79).
- Treatment persistence was significantly more frequent in the ustekinumab group (71.5% vs 49.7%; OR 2.54; 95% CI 1.40–4.62).
- The dose optimisation rate at week 48 was higher with vedolizumab (53.5% vs 30.1%; OR 0.37; 95% CI 0.21–0.67).
- Ustekinumab was associated with higher clinical remission rates in patients with ileal CD (OR 3.49; 95% CI 1.33–9.17), penetrating disease (OR 6.58; 95% CI 1.91–22.68) and a history of perianal disease (OR 2.48; 95% CI 1.04–5.93).
- Regardless of treatment group, combination therapy was associated with a higher clinical remission rate (OR 1.93; 95% CI 1.09–3.43).

In a comparable Dutch study, ustekinumab was also associated with higher efficacy than vedolizumab [2]. In a prospective registry specifically developed for comparative studies, a total of 128 vedolizumab- and 85 ustekinumab-treated patients fulfilled inclusion criteria, of which 69 patients in each group were then matched. The ustekinumab group was more likely to achieve corticosteroid-free clinical remission (OR 2.56; 95% CI 1.35–4.87; P=0.004), biochemical remission (OR 2.22; 95% CI 1.04–4.74; P=0.040), and combined corticosteroid-free clinical and biochemical remission (OR 2.58; 95% CI 1.15–5.78; P=0.022).

1. Alric H, et al. ECCO-IBD 2020, DOP80.
2. Biemans V, et al. ECCO-IBD 2020, DOP77.

Cancer Risk

Increased risk of small bowel cancer in IBD

In a population-based cohort of Swedish and Danish inflammatory bowel disease (IBD) patients, the risk of small bowel cancer was elevated compared with the general population, particularly among patients with Crohn's disease (CD). However, absolute risks were still low [1].

In previous studies, CD has been associated with increased small bowel cancer risk, but these studies were limited by multiple factors resulting in exaggerated relative risks and incidence data. Data on an association between ulcerative colitis (UC) and small bowel cancer are scarce. The Swedish-Danish cohort consisted of 161,896 patients diagnosed with IBD during 1969–2017 (CD, 47,370; UC, 97,515; unclassified IBD, 17,011) and matched reference individuals from the general population.

During follow-up, 237 cases of small bowel cancer were diagnosed in the IBD group (CD, 24.4/100,000 person-years; UC, 5.88/100,000 person-years), compared with 640 cases in reference individuals (CD reference group, 2.81/100,000 person-years; UC reference group, 3.32/100,000 person-years). This corresponds to one extra case of small bowel cancer in 385 CD patients, and one extra case in 500 UC patients, followed-up for 10 years. The adjusted hazard ratio for incident small bowel cancer was 9.09 (95% CI 7.34–11.3) and 1.85 (95% CI 1.43–2.39) in CD and UC patients, respectively. Relative risks among CD patients were highest for recently diagnosed, childhood-onset, ileal, and stricturing disease; among UC patients for those with extensive colitis and primary sclerosing cholangitis. In CD patients, the risk of all small bowel cancer subtypes was increased (aHR 15.8 for adenocarcinoma, 5.51 for neuroendocrine tumours, and 4.04 for sarcoma). In UC patients, only the risk of adenocarcinoma (aHR 1.99) and neuroendocrine tumours (aHR 2.01) were increased. The authors noted that further studies should evaluate the utility of small bowel cancer surveillance in selected populations.

1. Axelrad J, et al. ECCO-IBD 2020, OP08.

Increased incidence of colorectal cancer and death in CD

Patients with Crohn's disease (CD) have an increased risk of a colorectal cancer (CRC) and CRC-associated death [1]. CRC surveillance among CD patients could likely be improved, focusing on patients <40 years at CD onset, patients with colon inflammation, and patients with primary sclerosing cholangitis.

The aim of this nationwide register-based cohort study was to assess risks of tumour stage-adjusted incident CRC and CRC mortality among patients with CD compared with the general population. A total of 47,035 patients in Denmark (n=13,056) and Sweden (n=33,979) were compared with 463,187 matched reference individuals from the general population. During 1969–2017, 499 CD patients developed CRC (adjusted HR 1.40; 95% CI 1.27–1.53).

- In CD patients there were 296 (0.47/1000 person-years) deaths from CRC versus 1,968 (0.31/1000) in the reference group (HR 1.74; 95% CI 1.54–1.96).
- CD patients with CRC had a higher risk of CRC mortality than non-CD patients with CRC (HR 1.30; 95% CI 1.06–1.59) despite matched tumour stage at diagnosis.

- CD patients with ≥8 years of follow-up or who were diagnosed with primary sclerosing cholangitis had an increased overall risk of CRC death (HR 1.41; 95% CI 1.18–1.69) or CRC diagnosis (HR 1.12; 95% CI 0.98–1.28).
- In patients potentially eligible for CRC surveillance, risk of CRC death was only significantly increased in patients with CD onset <40 years, disease activity in the colon only, or with primary sclerosing cholangitis.

1. Olen O, et al. ECCO-IBD 2020, OP14.

Risk of rectal, anal cancer increased in perianal CD

In a Danish nationwide study, 17% of Crohn's disease (CD) patients developed perianal CD. The risk of rectal or anal cancer was increased in patients with perianal CD compared with non- inflammatory bowel disease (IBD) matched controls. These findings highlight the need for surveillance of rectal and anal cancer.

The aim of this study was to assess the incidence and course of perianal CD in adult patients, and to describe changes in medical and surgical management as well as rates of cancer [1]. The cohort comprised all individuals >18 years diagnosed with CD in Denmark within a 19-year period (1997-2016). Of 9,739 CD patients, 1,697 (17%) had perianal CD. Perianal fistulas accounted for 943 cases (56%). The overall incidence of perianal CD was 20/1,000 patient-years and remained stable over time. More patients with perianal CD than without were treated with immunomodulators (70% vs 51%; P<0.001) and biologics (35% vs 15%; P<0.001). The continuing high incidence of perianal CD suggests disease-modifying effects of biologics are limited, according to the authors. Patients with perianal CD had a significantly higher risk of undergoing major abdominal surgery than patients without perianal CD (HR 1.52; 95% CI 1.40-1.65; P<0.001).

The incidence rate ratios of anal and rectal cancer in perianal CD patients were 12.46 (95% CI 5.07-30.59; P<0.001) and 2.41 (95% CI 1.31-4.42; P=0.003) respectively, compared with non-IBD matched controls. The incidence rate ratios of anal and rectal cancer in perianal CD patients were 2.36 (95% CI 0.86-6.50; P=0.09) and 1.35 (95% CI 0.68-2.68; P=0.38) respectively, compared with CD patients without perianal CD.

1. Wewer MD, et al. ECCO-IBD 2020, OP12.

Glyco-fingerprint as risk factor of UC-associated cancer

A cross-sectional study revealed a distinct glycoimmuno-profile along the colitis-associated carcinoma cascade. It could represent a biomarker to identify ulcerative colitis (UC) patients at risk of UC-related cancer earlier [1].

The same group previously described differential expression of glycans in colitis and cancer contexts mediated by *MGAT5* glycogene [2]. The aim of the present study was to elucidate if this constitutes a new mechanism in colitis-associated carcinoma. A cohort of paraffin samples from colitis-associated carcinoma patients at different stages of carcinogenesis (colitis, dysplasia, colon cancer) were evaluated by immunohistochemistry. *In vivo* studies were conducted in *MGAT5* wild-type and knock-out mice.

Preliminary results showed a distinct glycoprofile in stroma, which is characterised by a decreased expression of branched N-glycans in colitis, followed by increased expression in dysplasia and colon carcinoma stages. This was corroborated by RNA sequencing analysis on colon of a colitis-associated cancer mouse model. Colonic T cells isolated from both *MGAT5* wild-type and knock-out mice also presented a distinct glycoprofile along colitis-associated carcinoma development.

1. Dias A, et al. ECCO-IBD 2020, OP13.
2. Dias AM, et al. Hum Mol Genet. 2014 May 1;23(9):2416-27.

Miscellaneous Topics

Resolution of mucosal inflammation has dramatic effect

In a retrospective cohort study, normalisation of faecal calprotectin (FCP) within 12 months of Crohn's disease (CD) diagnosis was associated with a reduced risk of disease progression [1]. According to the authors, their findings strongly support implementing treat-to-target strategies earlier than previously tested in CD.

The study was performed in a tertiary inflammatory bowel disease (IBD) centre in the United Kingdom, where all incident cases of CD diagnosed between 2005 and 2017 were identified. Included were patients with an FCP measurement of >250 µg/g at diagnosis who had at least 1 follow-up FCP measured within 12 months of diagnosis and with over 12 months of follow-up. A total of 375 patients were included with a median follow-up of 5.3 years.

Normalisation of FCP (<250 µg/g) within 12 months of diagnosis was confirmed in 163 patients (43.5%). These patients had a significantly lower risk of composite disease progression (HR 0.351; 95% CI 0.235–0.523; P<0.001). At 2, 5, and 7 years after diagnosis, cumulative rates of composite disease progression were 7.8%, 21.4%, and 29.9% in those who normalised their FCP, versus 22.8%, 50.7%, and 60.5% in those that did not. Normalisation of FCP was the only predictor that remained significant for all separate progression endpoints:

- progression in Montreal behaviour/new perianal disease (HR 0.250; 95% CI 0.122–0.512; P<0.001);
- hospitalisation (HR 0.346; 95% CI 0.217–0.553; P<0.001);
- surgery (HR 0.370; 95% CI 0.181–0.755; P=0.006).

According to the authors, the immediate implication for healthcare providers and patients is that by ensuring resolution of mucosal inflammation –measured by proxy with FCP, and regardless of other variables– within 1 year of diagnosis, has a dramatic effect on the course of the disease.

1. Plevris N, et al. ECCO-IBD 2020, DOP11.

PICaSSO validated in real-life study

In a validation study, PICaSSO (Paddington International Virtual ChromoendoScopy ScOre) accurately predicted histological healing and long-term remission and can be a useful tool in the management of ulcerative colitis (UC) [1].

The newly published PICaSSO characterises subtle mucosal and vascular changes and defines mucosal healing, which has become an important goal in UC treatment. In a real-life study, PICaSSO was validated and its ability to predict relapse assessed. A total of 278 patients with UC were prospectively recruited from 11 international centres. Participating endoscopists received training on PICaSSO. For histological assessment, Robarts (RHI) and Nancy histological indexes (NI) were used.

Table. Sensitivity, specificity, and accuracy in predicting histological healing [1]

Score	RHI ≤3 (95% CI)	NI ≤1 (95% CI)
PICaSSO total ≤8		
Sensitivity	94.6% (71.9–97.6)	78.8% (37.4–86.6)
Specificity	57.7% (32.7–66.9)	64.8% (28.5–73.6)
Accuracy	79.9% (70.0–93.5)	67.6% (63.3–71.2)
PICaSSO mucosal architecture ≤3		
Sensitivity	93.4% (81.8–97.6)	97.1% (56.5–99.4)
Specificity	56.8% (41.4–66.7)	63.9% (35.6–73.1)
Accuracy	78.8% (72.4–82.7)	84.2% (72.9–88.0)
PICaSSO vascular architecture ≤3		
Sensitivity	74.9% (51.2–84.5)	78.8% (37.4–86.6)
Specificity	65.8% (55.1–74.2)	73.1% (61.8–80.6)
Accuracy	71.2% (67.0–74.6)	76.6% (72.0–79.6)
UCEIS score ≤1		
Sensitivity	91.6% (77.6–95.8)	93.5% (57.8–97.8)
Specificity	60.4% (45.0–68.5)	64.8% (53.1–73.1)
Accuracy	79.1% (73.3–82.6)	82.3% (77.9–85.6)

RHI, Robarts histological indexes; NI, Nancy histological indexes; UCEIS, Ulcerative Colitis Endoscopic Index of Severity

The diagnostic performance of PICaSSO in predicting histological healing is shown in the Table. A PICaSSO of ≤3 for mucosal and vascular architecture resulted in a fair to good prediction of healing, both by RHI and NHI. A total PICaSSO of ≤8 and an Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score of ≤1 also predicted remission after 1 year. A Kaplan–Meier curve showed a favourable chance of survival without relapse with a PICaSSO of ≤8.

1. Iacucci M, et al. ECCO-IBD 2020, OP26.

Re-inducing inflammation in organoids from UC patients

Patient-derived intestinal organoids provide a powerful tool to better understand mechanisms underlying inflammatory bowel disease (IBD), but patient-specific organoids quickly lose their inflammatory phenotype. A Belgian group showed that inflammation can efficiently be (re-)induced in organoids from ulcerative colitis (UC) patients as well as non-IBD individuals [1].

First author Kaline Arnauts (Catholic University of Leuven, Belgium) explained the hypothesis that in order to study UC in an *ex vivo* model, inflammation should be re-induced towards levels corresponding to the *in vivo* situation. The researchers also wanted to know if organoids derived from inflamed regions are relatively sensitive to inflammatory stimulation. They therefore obtained biopsies from 8 patients with active UC, both from inflamed and non-inflamed regions, and from 8 non-IBD controls.

Exposure to the inflammatory mix induced transcriptional activation of inflammatory genes (including *CXCL1*, *DUOXA2*, *IL1β*, *IL8*, and *IL23α*; all P<0.001) and pathways in all conditions. Organoids of non-IBD controls clustered separate from organoids of UC patients. However, Arnauts added that organoids from inflamed and non-inflamed regions in UC patients were indistinguishable, also after inflammatory stimulation. She concluded: "To study UC in an *ex vivo* model, inflammation should be re-introduced prior to evaluation of other mechanisms. It is, however, not essential for organoid cultures to be obtained from biopsies from inflamed regions in UC patients."

1. Arnauts K, et al. ECCO-IBD 2020, OP11.

Role of immune cells in intestinal fibrosis

The relative contribution of innate and adaptive immune cells in the mucosa and deeper layers in fibrotic distal ileum of Crohn's disease (CD) patients was assessed. The results show that inflammation in the deeper intestinal layers is different from the inflammatory signature seen in mucosal inflamed regions [1].

There is an urgent need for the identification of pathways and markers involved in fibrogenesis. As intestinal fibrosis mainly occurs in the deeper intestinal layers, immune cell characterisation of mucosal and deeper intestinal layers of the ileum was performed. The resected ileum of 17 CD and 6 colorectal cancer (CRC) patients undergoing right hemicolectomy were collected and divided in macroscopically inflamed and fibrotic tissue.

In 12 CD patients, an additional macroscopically inflamed region next to the fibrotic area was identified, with a lower fibrosis score than in the fibrotic area (4.0 vs 6.0; P=0.016). Both fibrotic and inflamed regions showed increased inflammation versus proximal unaffected CD and control (non-IBD) ileum (4.0 and 4.5 vs 1.0 and 0.0; P<0.001 for all). In the inflamed ileum, no differences in immune populations were observed between mucosa and deeper layers. In contrast, CD19-positive B cells were specifically enriched in fibrotic ileum versus proximal CD mucosa (32.2% vs 20.4% of CD45-positive cells; P=0.008). In the deeper layers of fibrostenotic CD ileum, alternative innate immune cells, such as mature CD11c-postive dendritic cells (P=0.042) and CD206-positive macrophages (P<0.001), were enriched compared to the mucosa overlying the fibrotic tissue. The authors concluded that, as these cells are specifically expanded in the deeper intestinal layers, this finding may lead to identifying targets for new anti-fibrotic therapies.

1. Creyns B, et al. ECCO-IBD 2020, DOP83.

Association between meat consumption and IBD risk

Animal protein intake is associated with the risk of inflammatory bowel disease (IBD) in the European Prospective Investigation into Cancer and Nutrition – Inflammatory Bowel Diseases (EPIC-IBD) cohort [1]. The investigators said the observed associations between the consumption of meat –red meat in particular– and the risk of ulcerative colitis (UC) and IBD warrant further investigation.

The association between high protein intake and risk of IBD was investigated in the EPIC-IBD cohort, which is embedded in the main EPIC study (n=521,000). In the presented analysis, 413,593 participants were included.

After a mean follow-up of 16 years, 595 incident cases of IBD were identified: 418 cases of UC and 177 cases of Crohn's disease (CD). There was no association between total protein intake and risk of IBD (adjusted HR for the fourth versus vs first quartile 1.25; 95% CI 0.89–1.77; P-trend=0.33). The association between the calibrated continuous variable of animal protein intake and IBD risk was significant, however

(aHR per 10 g/day 1.10; 95% CI 1.00–1.21). There was no association between vegetable protein intake and IBD risk. Meat consumption and IBD risk were found to be associated (aHR for the fourth vs first quartile 1.37; 95% CI 1.02–1.82; P-trend=0.003). The same was true for red meat consumption and IBD risk (aHR for the fourth vs the first quartile 1.41; 95% CI 1.03–1.92; P-trend=0.006). There was an association between total meat, as well as red meat, and risk of UC. No association was found between animal proteins and risk of CD.

1. Dong C, et al. ECCO-IBD 2020, OP17.

CD exclusion diet corrects dysbiosis

Why does dietary therapy induce remission, reduce inflammation and induce compositional changes in the microbiome in Crohn's disease (CD)? Whole metagenome analysis revealed dietary therapy corrected dysbiosis towards healthy controls [1].

There were 2 study groups: one on the CD Exclusion Diet (CDED) and partial enteral nutrition (PEN), the other one using Exclusive Enteral Nutrition (EEN). In 178 samples from 70 participants, whole metagenome and 16S rDNA sequences were obtained at baseline, week 6, and week 12. For metagenome analysis, the groups were further divided into patients achieving intention-to-treat (ITT)-remission at week 6 (CDED+PEN: 31/38 and EEN: 23/32) and those who did not. At baseline, Proteobacteria were significantly higher in samples of active CD compared to healthy controls.

Dietary therapy decreased the relative abundance of genera from Proteobacteria towards those of healthy controls. CDED+PEN remission was associated with a significant increase in Clostridiales. Diet-induced remission (with either CDED+PEN or EEN) at week 6 was associated with a decrease in Proteobacteria: the relative abundance of Proteobacteria (e.g. *Escherichia*, *Klebsiella*, and *Citrobacter*) was significantly lower than at baseline, but still more outspoken in CD patients; Bacilli and Firmicutes remained more predominant in samples of healthy persons. The researchers noted that sustained dietary therapy beyond 6 weeks with CDED+PEN avoided 'rebound' in disease-associated species, notably Proteobacteria, when the oral diet was reintroduced. Continued CDED+PEN between week 6 and 12 was associated with a further decrease in Proteobacteria. *Faecalibacterium* became more abundant in CD by week 12, as did *Blautia* and *Sutterella*. *Anaerostipes*, *Ruminococcus*, Bacilli, Porphyromonadaceae, Bifidobacteriales, Ascomycota, and Caudovirales were more abundant in healthy samples than in the CDED+PEN group at week 12.

1. Van Limbergen, et al. ECCO-IBD 2020, OP22.