Medicom International Conference Series in Gastroenterology

14th Congress of ECCO

European Crohn's and Colitis Organisation

6-9 MARCH 2019 • COPENHAGEN • DENMARK

PEER-REVIEWED CONFERENCE REPORT

Many compounds in development

ECCO 2019 saw positive preclinical, phase 1 and 2 trial results of many new compounds, such as a MAdCAM-1 antibody and a p19-directed IL-23 antibody; as well as a cyclosporine comeback.

read more on PAGE 3

Head-to-head comparison of two biologicals

For the first time, two biological treatments of UC were directly compared in a randomised trial. Vedolizumab was superior to adalimumab in achieving clinical remission and mucosal healing.

read more on PAGE 7

Cost-saving effect of biologicals

The first-ever prospective long-term analysis of healthcare costs in European IBD-patients in the era of biologicals indicated a cost-saving effect of biologicals, despite their high acquisition costs.

read more on PAGE 16

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Editor Dr Triana Lobatón Ortega, University Hospital Ghent, Belgium

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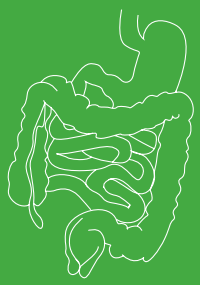

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Letter from the Editor

Dr Triana Lobatón Ortega

Dear Reader,

The management of IBD is dramatically changing in the last years mainly because of the availability of new treatments. At the 14th ECCO Congress we have seen the long-term results of many of those such as ustekinumab (for UC), vedolizumab, and tofacitinib. Also, results of newer compounds such as Pan-Janus kinase inhibitor TD-1473, etrasimod, mirikizumab, and upadacitinib, amongst others. Importantly, the results from the VARSITY trial were presented, the first head-to-head trial with biologicals in IBD.

Together with the clinical trials, the scientific community is making a great effort in order to optimize our strategies of managing IBD. An excellent example is the CALM study, demonstrating that T2T does have an impact on the outcome of the disease (in this case for CD). Similar studies are urgently needed, since properly using the treatments we have is as important as developing new ones.

In addition, the physiopathology and genetics of IBD remain a research challenge and the role of microbiota is in this context a hot topic, including interesting new studies. The glycans as novel immunomodulators of T cell-mediated immune response were also presented with promising results. Finally, the results of a new topical review focused on complementary and alternative medicine were also presented.

In sum, the variety and quality of abstracts presented was excellent and in the present report you can find an accurate selection of them.

Best Regards,
Triana Lobatón

Biography

Triana Lobatón works as a full-time gastroenterologist at the IBD Unit of the Department of Gastroenterology at Ghent University Hospital (Belgium). She finished her training as gastroenterologist at Bellvitge University Hospital (Barcelona, Spain). During her training, she spent 2 moths (in 2010) at Mount Sinai University Hospital in NY (US). She obtained her PhD at the University of Barcelona in 2015. As part of her PhD program, she spent 18 months (2013-2014) at Leuven University Hospital (Belgium) under the supervision of Prof. Séverine Vermeire. Her clinical activity and research is focused on IBD, in particular clinical projects. She has been coordinator of the young GETECCU (Spanish group of Crohn and Colitis), and is also involved in several ECCO activities such as the e-courses.

Interview with
Prof. Janneke van der Woude, MD,

conducted on 9 March 2019 in Copenhagen, Denmark, by Michiel Tent

Prof. Van der Woude is a gastroenterologist specialised in IBD at the Erasmus University Medical Center in Rotterdam, the Netherlands, as well as chair member of the organising committee of the 14th edition of the ECCO meeting.

Prof. Van der Woude, this is the largest ECCO meeting ever with over 8,000 attendees from 84 countries. Why does this meeting attract so many participants from all over the world?

"We are very happy to attract so many attendants from all corners of the globe. I think part of it has to do with the increase in the incidence of IBD worldwide, including countries like China and Japan. Consequently, gastroenterologists worldwide are interested in the latest news regarding treatments in the field of IBD."

Compared with previous editions, what is new about the way this year's meeting is organised?

"I think the organising committee is doing a really good job, implementing a few changes this year but not too many. There are numerous opportunities for everyone to be updated on different topics regarding IBD, ranging from, for example, imaging to clinical trial updates. There is something for everyone."

Of all the topics that are presented here, which ones would you like to draw our special attention to?

"It is very difficult to choose because IBD is such a complicated condition with so many important aspects, such as quality of life, advances in treatment, and basic research into the causes of IBD."

What are the biggest challenges in the field?

"We still have to further improve our patients' quality of life: they still complain about things like fatigue and intestinal pain. We have to listen to them better, and ensure they are involved in clinical studies whenever possible. We still do not have that many options to treat the really invalidating consequences of Crohn's disease or ulcerative colitis. All our efforts and research will hopefully result one day in finding the 'holy grail', being a cure for IBD. In an even more distant future, we would also like to be able to predict who will get IBD, enabling very early intervention."

You mentioned curing IBD; where do you think we will stand in 5 or 10 years? Will a cure be available by then?

"That may be a little too optimistic; I have been hoping to see a cure for IBD for 20 years already. At any rate, we are gaining insight into the pathogenesis of IBD. We may be able to better select specific patient groups for specific targeted treatments; resulting if not in curing the disease, at least in treating it more effectively at an early stage."

New Compounds: Study Results

HDAC6 inhibition by CKD-506

CKD-506 has been found to have therapeutic effects in various colitis animal models. Therefore, this oral selective histone deacetylase 6 (HDAC6) inhibitor may exert beneficial effect in patients with Crohn's disease and ulcerative colitis. The effect of CKD-506 on rheumatoid arthritis is already being evaluated in a clinical phase 2 study.

In the preclinical study presented at ECCO 2019, HDAC6 was overexpressed in colon tissue of patients with Crohn's disease and ulcerative colitis [1]. *In vitro,* HDAC6 overexpression by plasmid DNA strongly induced the production of various inflammatory mediators, especially TNFα, IL-6, IP-10, and ROS production from macrophages. However, CKD-506 inhibited HDAC6-mediated inflammatory responses in macrophages through NF-κB and AP-1. *In vivo,* CKD-506 strongly inhibited disease activity indexes in DSS-, TNBS-, piroxicam- (IL-10−/−)-, and adaptive T cell transfer-mediated colitis. In acute colitis models, CKD-506 inhibited IL-6 and TNFα expression in colon tissue of DSS-induced colitis; it also inhibited ICAM-1, VCAM-1, and IP-10 expression in colon tissue of a TNBS-induced colitis model. In addition, CKD-506 inhibited IκB phosphorylation, IL-6, and TNFα expression in colon tissue and mononuclear cells of lamina propria in piroxicam-induced colitis of IL-10−/− mice. Moreover, CKD-506 inhibited various inflammatory cytokines in serum as well as in colon tissue of T cell adaptive transfer colitis of RAG−/− mice.

1. Shin J, et al. ECCO 2019, OP23.

Selective oral sphingosine 1-phosphate receptor modulator amiselimod

Amiselimod (AMS) is a new selective oral sphingosine 1-phosphate (S1P) receptor modulator, which is being developed for the treatment of various autoimmune-mediated diseases, including Crohn's disease. In a prospective, randomised, placebo-controlled clinical trial, treatment of refractory Crohn's disease with AMS 0.4 mg for 12 weeks was generally well-tolerated, without any new safety sigals [1]. No effect was found on clinical or biochemical disease activity.

Of 78 randomised patients, 28/40 patients on AMS and 33/38 on placebo completed the 14-week induction trial. The primary endpoint Crohn's Disease Activity Index (CDAI)100 was attained in 19/39 (48.7%) on AMS and in 20/37 (54.1%) on placebo. CDAI 70 and clinical remission (CDAI <150) were observed in 21/39 (53.8%) and 11/39 (28.2%) on AMS and in 24/37 (64.9%) and 15/37 (40.5%) on placebo, respectively. No clinically meaningful differences were observed in serum C-reactive protein concentrations and faecal calprotectin in either group. Mean lymphocyte counts on AMS showed significant reduction by week 4 (47.7% of baseline), after which they reached graphical plateau. The authors considered the high placebo response and weaker lymphocyte reduction to contribute to the negative efficacy results in this study.

1. D'Haens G, et al. ECCO 2019, DOP48.

Pan-Janus kinase inhibitor TD-1473

Oral TD-1473 is a gut-selective pan-Janus kinase (JAK) inhibitor. In a double-blind, placebo-controlled, multicentre, phase 1b study, oral TD-1473 results in low systemic exposure and high concentration in gut tissue at doses up to 270 mg [1]. Signals for clinical, endoscopic, histological, and biomarker activity were observed in subjects with moderately to severely active ulcerative colitis after 4 weeks of treatment with TD-1473 at all 3 doses (i.e. 20 mg, 80 mg, and 270 mg).

The 40 enrolled subjects received placebo (n=9), TD-1473 20 mg (n=10), 80 mg (n=10), or 270 mg (n=11) once daily for 28 days. Trends were observed of higher rates of clinical response, endoscopic healing, and improvement by ≥1 point in rectal bleeding and endoscopy subscores with TD-1473 relative to placebo. Serum C-reactive protein decreased relative to placebo at all dose levels. Faecal calprotectin decreased in subjects treated with 80 mg and 270 mg. Four weeks of treatment with TD-1473 at 20 mg and 270 mg was associated with dose-related reductions in Robarts' Histologic Index (RHI), along with colonic levels of phospho-STAT1 and phospho-STAT3 proteins, which reached statistical significance in the 270 mg group. RNA-

sequencing analysis suggested that TD-1473 has a local effect on the ulcerative colitis-transcriptomics signature.

1. Sandborn W, et al. ECCO 2019, DOP53.

Selective sphingosine-1-phosphate receptor modulator etrasimod

Etrasimod (APD334) is an oral, selective sphingosine-1-phosphate receptor modulator. It was evaluated in the randomised, double-blind, placebo-controlled, parallel-group, phase 2 OASIS study in patients with moderately to severely active ulcerative colitis [1]. Etrasimod 2 mg induced significantly higher rates of endoscopic improvement, histological improvement and remission, and mucosal healing in ulcerative colitis patients compared with placebo.

The 156 participants were randomised to once-daily etrasimod 1 mg (n=52), 2 mg (n=50), or placebo (n=54); 90% of patients completed the study. At week 12, etrasimod 2 mg, compared with placebo, resulted in significantly higher rates of:

- endoscopic improvement (43.2% vs 16.3%; P=0.003);
- histological improvement (31.7% vs 10.2%; P=0.006);
- histological remission (19.5% vs 6.1%; P=0.027).

Mucosal healing (defined as both endoscopic improvement and histological remission) was seen in 19.5% and 4.1% of patients treated with etrasimod 2 mg and placebo, respectively (P=0.010). The authors think mucosal healing may prove to be an achievable and objective measure of drug efficacy in ulcerative colitis induction studies.

1. Peyrin-Biroulet L, et al. ECCO 2019, OP09.

p19-directed IL-23 antibody mirikizumab

Mirikizumab is a p19-directed IL-23 antibody. It has demonstrated efficacy and was well-tolerated during 12 weeks of induction treatment in a phase 2 randomised clinical trial [1]. Results through week 52 from this trial demonstrated durable efficacy, with no unexpected safety signals and few discontinuations due to AEs throughout the maintenance period [2].

Patients who achieved clinical response to mirikizumab at week 12, were re-randomised to receive mirikizumab 200 mg subcutaneously every 4 (n=47) or every 12 weeks (n=46) through week 52. At baseline, 52.7% had previously received a biologic. The main results at week 52 for the respective groups were as follows:

- 46.8% and 37.0% were in clinical remission;
- 80.9% and 76.1% had clinical response;
- 57.4% and 47.8% had an ES 0/1;
- 61.1% and 38.5% of those in clinical remission at week 12 remained in clinical remission at week 52; and
- 37.9% and 36.4% of those with clinical response, but not in remission, at week 12 achieved clinical remission at week 52.

During the maintenance period, 1 patient discontinued the study due to an adverse event, and similar frequencies of treatment-emergent adverse events and serious adverse events were reported across both treatment groups. This is the first data demonstrating that a p19-directed IL-23 antibody may be an effective maintenance therapy in patients with moderately to severely active ulcerative colitis.

1. Reich K, et al. Br J Dermatol. 2019 Feb 7. doi: 10.1111/bjd.17628. [Epub ahead of print]
2. Geert G, et al. ECCO 2019, OP38.

OPERA II study: MAdCAM-1 antibody SHP647

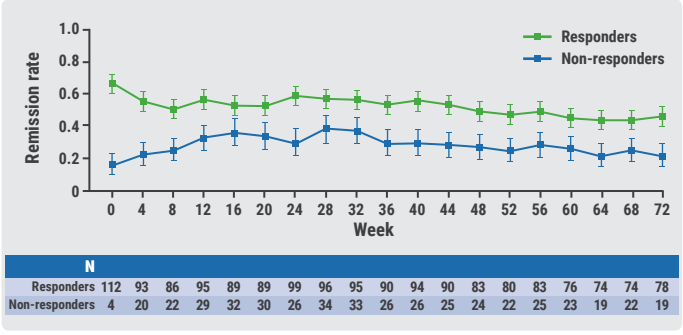
SHP647 is a fully human IgG2 anti-mucosal addressin cell adhesion molecule 1 (MAdCAM-1) antibody in development for the treatment of Crohn's disease. In the extension study of the placebo-controlled OPERA II trial, remission rates were sustained over 72 weeks with SHP647, regardless of initial response to induction treatment or dose-escalation status [1].

Patients enrolled in OPERA II completed either 12 weeks induction treatment (placebo or SHP647 22.5 mg, 75 mg, or 225 mg subcutaneous) in the OPERA trial regardless of response or had a clinical response to SHP647 225 mg in the TOSCA trial. In OPERA II, they received SHP647 (75 mg) every 4 weeks from week 0–72 and were followed up monthly for safety for a further 24 weeks. Dose reduction to 22.5 mg or escalation to 225 mg was allowed from week 8 as judged by the investigator. High-sensitivity C-reactive protein (hsCRP), faecal calprotectin (FC), and Harvey-Bradshaw Index (HBI) score were assessed as exploratory efficacy endpoints.

Out of 268 participants, 149 completed the study. Remission rate (HBI <5) initially decreased in responders and increased in non-responders from baseline to week 8; it was then maintained in both groups to week 72 (see Figure). No patient de-escalated the dose, but 157 patients escalated to 225 mg. Those who escalated had slightly higher hsCRP and FC concentrations at baseline than those who remained on

75 mg (mean hsCRP, 22.8 vs 20.5 µg/ml; mean FC, 2,662.7 vs 1,988.8 mg/kg). hsCRP and FC levels were higher in patients who dose-escalated than those who remained on 75 mg subcutaneous, which adds to the evidence for long-term efficacy of SHP647.

Figure: Change over time in OPERA II in mean remission rate (HBI score <5) for responders and non-responders to treatment with SHP647 from OPERA and TOSCA trials [1]



Includes all patients who escalated dose to 225 mg and those who remained on 75 mg SHP647

1. D'Haens G, et al. ECCO 2019, OP08.

Upadacitinib: data from U-ACHIEVE and CELEST

Upadacitinib is an oral, selective Janus kinase 1 inhibitor. In a dose-ranging phase 2b/3 induction study, upadacitinib consistently demonstrated significant improvement in endoscopic and histological outcomes as well as mucosal healing compared with placebo in patients with moderately to severely active ulcerative colitis [1]. In moderate-to-severe Crohn's disease, upadacitinib numerically reduced extra-intestinal manifestations [2].

Patients (n=250) with an adapted Mayo score of 5 to 9 points and centrally read endoscopy subscore of 2 to 3 were randomised to receive placebo or extended-release upadacitinib 7.5 mg, 15 mg, 30 mg, 45 mg once daily for 8 weeks. At baseline, 77.6% had used biologics before, 36% had an adapted Mayo score of >7, and 79% had an endoscopic subscore of 3. At week 8, a dose-response relationship was observed for all efficacy endpoints. The proportion of patients achieving endoscopic improvement, endoscopic remission, histological improvement, histological remission, and mucosal healing was statistically significantly higher (P<0.05) in the upadacitinib 30 mg and 45 mg groups than in the placebo group (see Table 1).

Table 1: Proportion of patients achieving efficacy endpoints at week 8 [1]

Endpoints, n (%)	Placebo n=46	upadacitinib 7.5 mg QD n=47	upadacitinib 15 mg QD n=49	upadacitinib 30 mg QD n=52	upadacitinib 45 mg QD n=56
Endoscopic improvement	1 (2.2)	7 (14.9)*	15 (30.6)***	14 (26.9)***	20 (35.7)***
Endoscopic remission	0	3 (6.4)	2 (4.1)	5 (9.6)*	10 (17.9)**
Histologic improvement	3 (8.1)	15 (35.7)**	25 (55.6)***	23 (52.3)***	27 (56.3)***
Histologic remission	1 (2.6)	6 (13.6)+	11 (24.4)**	16 (35.6)***	23 (45.1)***
Mucosal healing	0	1 (2.1)	1 (2.0)	3 (5.8)*	8 (14.3)*

***, **, *, + statistically significant at 0.001, 0.01, 0.05, and 0.1 levels, respectively. QD, once daily

In Crohn's disease patients participating in the CELEST study, a numerical resolution in extra-intestinal manifestations (EIMs) was observed with upadacitinib, suggesting a clinical benefit induced by upadacitinib. CELEST was a multicentre, randomised, double-blind, placebo-controlled, phase 2 study in 220 adults with moderate-to-severe Crohn's disease and inadequate response/intolerance to immunosuppressants or TNFi. Patients were randomised to 16-week induction therapy with placebo or Crohn's disease 3 mg, 6 mg, 12 mg, or 24 mg twice daily or 24-mg once daily. The presence of EIMs was recorded at baseline and week 16.

Out of 220 patients, 111 (50.5%) had at least 1 EIM at baseline; 31 (28%) of these had 2 or more EIMs. Patients who had at least one EIM at baseline had median (min-max) Crohn's Disease Activity Index (CDAI) 295 (222–447), and Crohn's Disease duration of 10.8 (0.1-44.7) years; 85 (96.6%) had failed 1 or more TNFi. The most commonly reported EIMs were peripheral and/or axial arthropathies (n=87), anaemia (n=31), and oral aphthous ulcers (n=11). At week 16, compared with placebo, a numerically greater proportion of patients achieved resolution of any EIM, classic EIMs, and arthropathy with upadacitinib 12 mg and 24 mg twice daily, and upadacitinib 24 mg once daily doses (see Table 2).

Table 2: Proportion of patients achieving resolution of any EIMs, and arthropathy at week 16 [2]

Endpoints, n (%)	Placebo n=23	3 mg BID n=26	6 mg BID n=15	12 mg BID n=11	24 mg BID n=21	24 mg QD n=15
Resolution of any EIMS	7/23 (30.4)	10/26 (38.5)	4/15 (26.7)	6/11 (54.5)	11/21 (52.4)	7/15 (46.7)
Resolution of arthropathy	5/17 (29.4)	10/24 (41.7)	3/12 (25.0)	3/7 (42.9)	9/16 (56.3)	6/11 (54.5)

Data are reported in the modified intent-to-treat population. Resolution of extra-intestinal manifestations (EIMs) was defined as zero EIMs at week 16

1. Sandborn J, et al. ECCO 2019, OP14.
2. Peyrin-Biroulet L, et al. ECCO 2019, DOP50.

ABX464: HIV drug tested in ulcerative colitis

HIV studies have already shown the potent anti-inflammatory properties of ABX464, impacting the expression of miR124. In a first-in-disease phase 2a study, ABX464 was tested in patients with moderate-to-severe ulcerative colitis who were intolerant and/or refractory to existing treatments [1]. ABX464 50 mg once daily orally for 8 weeks was found to be safe and well tolerated. Clinical, endoscopy, histopathology, and biomarker analyses all showed consistent changes in favour of ABX464.

The study was performed in 32 patients from 15 European centres. A total of 29 (90.6%) patients (20 randomised to ABX464 and 9 to placebo) completed the induction study. The overall safety of ABX464 was very good, with no serious adverse events. The safety profile was similar to that seen in the clinical development in the HIV indication. The main efficacy results are presented in the Table.

Table: ABX464-101 study endpoints results after 56 days [1]

	ABX464 (n=20)	Placebo (n=9)	P-value
Clinical remission	35.0%	11.0%	0.16
Endoscopic improvement	50.0%	11.0%	0.03
Clinical response	70.0%	33.0%	0.06
Total Mayo score reduction	-53.0%	-27.0%	0.03
Partial Mayo score reduction	-62.0%	-32.0%	0.02
Faecal calprotectin decrease >50.0%	75.0%	50.0%	
miRNA124-fold expression	7.69	1.46	0.004

After the blinded induction phase, patients had the option to enrol in a 52-week, open-label, 50 mg once daily ABX464 study. The interim data from this maintenance study (n=22) shows further improvement in partial Mayo score and reduction in faecal calprotectin. This data supports a phase 2b multicentre, placebo-controlled, dose-ranging study in ulcerative colitis and a phase 2a study in Crohn's disease.

1. Vermeire S, et al. ECCO 2019, OP21.

Cyclosporine: novel low-dose, controlled-release formulation

Cyclosporine is effective in acute severe ulcerative colitis. However, concerns regarding systemic toxicities have limited its role to short-term induction therapy and as a bridge to other therapies. ST-0529 is a novel low-dose, controlled-release formulation of cyclosporine that was shown safe and well-tolerated in a phase 2a pilot study [1].

The phase 2a pilot study with 118 patients with mild or moderate ulcerative colitis, receiving 75 mg ST-0529 once daily, showed a numerically higher but not statistically significant difference in remission rate compared with placebo (13.2% vs 6.3%, P=0.22) after 4 weeks of treatment. Rates of clinical response were 30.2% and 18.8% (P=0.19). No differences were observed between the treatment groups for mucosal and histological healing. In the post hoc analysis, differences in the clinical response between treatment subgroups achieved statistical significance in some subgroups, with the largest clinical response rate seen in moderate ulcerative colitis patients taking 5-aminosalicylates and/or steroids. These preliminary data support further development of ST-0529 as a treatment for the induction and maintenance of remission in ulcerative colitis patients with moderate to severe disease.

1. Bloom S, et al. ECCO 2019, OP16.

Short-term and Long-term Treatment Results

The right drug for the right patient

The ever-increasing armamentarium for the treatment of inflammatory bowel disease (IBD) poses an 'embarrassment of riches', as Dr Charlie Lees (Western General Hospital, United Kingdom) put it. He discussed stratification by disease biology to choose the right drug for the right patient.

It has been neglected for too long that IBD is progressive, according to Dr Lees; the typical pattern being: Patients are diagnosed with active disease, remission is induced but without properly controlling inflammation, the disease will flare and evolve over time. "Once we realise we must not only treat symptoms but also underlying inflammation, we can finally change the natural history of the disease course and offer our patients a much better outlook," he said. "This means treating early, reducing flare rate, and getting close to a cure for some of our patients. Therefore, early control is everything." Proof for this concept has emerged from numerous studies of drugs emerging after anti-TNF.

However, not every patient needs a biological and/or maintenance therapy. How to stratify those patients who do? Dr Lees believes that "turbo-charged treat-to-target with precision medicine" is the right strategy no matter what the choice of therapy will be. Three steps are essential:

1. *Stratify therapy by risk factors,* such as smoking, extensive small bowel disease, and peri-anal disease. New ways to help stratification in a less 'crude' manner are emerging. Genetics are not yet the answer because there is no clinical utility yet. Another way is using transcriptomics, which seem to become clinically meaningful already. The results of the ongoing PROFILE trial (www.crohnsprofiletrial.com) will be very important.
2. *Stratify by biology.* Dr Lees: "Will we go for head-to-head trials, and/or allow ourselves the scientific luxury of going back to disease biology to properly understand how to stratify the choice of our medication?"
3. *Prevent disease flair.* Dr Lees mentioned the PREdiCCt study (www.predicct.co.uk) he is involved in, which looks at how environmental factors, diet, and the gut micro-organisms influence IBD flare and recovery.

Vedolizumab superior to adalimumab in ulcerative colitis

One of the most anticipated events of ECCO 2019 was the presentation of the head-to-head trial comparing the efficacy and safety of two biological agents [1]. In patients with moderately to severely active ulcerative colitis, vedolizumab was found to be superior to adalimumab in achieving clinical remission and endoscopic mucosal healing after 1 year. Both treatments were generally safe and well tolerated.

VARSITY was a phase 3b randomised, double-blind, double-dummy, multicentre, active-controlled trial. The 771 participants were randomised to: 1) active vedolizumab intravenous (IV) infusions (300 mg)/placebo subcutaneous injections; or 2) placebo IV infusions/active adalimumab subcutaneous injections (160 mg, 80 mg, 40 mg). The primary endpoint was clinical remission.

The results were presented by Dr Stefan Schreiber (University-Hospital Schleswig-Holstein, Germany), who showed that the percentage of patients who completed the study was 74.5% in the vedolizumab group vs 61.9% in the adalimumab group. Overall clinical remission rates at week 52 were 31.3% for vedolizumab and 22.5% for adalimumab (P=0.0061). Mucosal healing at week 52 was achieved in 39.7% and 27.7% of patients, respectively (P=0.0005). Overall, 62.7% and 69.2% of patients experienced an adverse event. Serious adverse events occurred in 11.0% and 13.7% of patients, respectively.

Dr Schreiber noted that the clinical superiority of vedolizumab was most pronounced in the anti-TNF naïve subpopulation in a subgroup analysis. Treatment differences in clinical response appeared to emerge between week 6 and week

14. Corticosteroid-free remission rates numerically favoured adalimumab, while the absolute reduction of corticosteroid use was greater with vedolizumab; however, treatment group differences were not significant. Both drugs were found to be generally safe and well-tolerated. Dr Schreiber concluded: "These results support the use of vedolizumab prior to adalimumab in patients with moderately tot severely active ulcerative colitis."

1. Schreiber S, et al. ECCO 2019, OP34.

Vedolizumab: Results from the GEMINI programme

The final results of GEMINI long-term safety suggest that vedolizumab has a safety profile suitable for long-term treatment of ulcerative colitis (UC) and Crohn's disease (CD). In this multi-national, multicentre, open-label, phase 3 study, no unexpected or new safety concerns emerged [1].

A total of 894 patients with UC and 1,349 with CD enrolled in GEMINI long-term safety for a planned treatment duration of 9 years. All patients had received ≥1 prior conventional therapy. Adverse events (AEs) occurred in 93% of UC patients and 96% of CD patients; most frequent were UC (36%) and CD (35%) exacerbations and nasopharyngitis (UC, 28%; CD, 25%). No new trends were observed for infections, malignancies, infusion-related reactions, or hepatic events. Serious AEs were reported in 31% of UC patients and 41% of CD patients; disease exacerbation being the most frequent serious AEs in both cohorts (UC, 13%; CD, 17%). Vedolizumab was discontinued due to AEs in 15% of UC patients and 17% of CD patients; the most frequent reason being UC or CD exacerbation (9% and 8%, respectively). No cases of progressive multi-focal leukoencephalopathy were seen. There were 10 deaths (UC, 4; CD, 6) during the study.

Other results from the GEMINI programme that were presented at ECCO 2019 include the following:

1. Long-term treatment with vedolizumab was associated with low immunogenicity rates (consistent with results from GEMINI 1 and 2), even in patients initially treated with vedolizumab induction followed by placebo maintenance in GEMINI 1 and 2 who were subsequently re-treated with vedolizumab in GEMINI long-term safety. No relationship was observed between immunogenicity and safety [2].
2. For induction therapy in patients with moderate-to-severe CD, combined therapy with vedolizumab and ongoing corticosteroid may be a synergistic approach, with a similar safety profile, compared with continued corticosteroid use alone or vedolizumab without ongoing corticosteroid use [3].
3. Can vedolizumab reduce surgical rates in patients with UC and CD? In an analysis of 834 patients from 3 trials (GEMINI I, III, and long-term safety), surgery rates were lower in the vedolizumab than in the placebo group in the first year of observation. In UC, this difference reached statistical significance. For patients who continued treatment for up to 5 years, vedolizumab provided long-term benefit in both diseases with low rates of surgical intervention [4].

1. Vermeire S, et al. ECCO 2019, OP26.
2. Wyant T, et al. ECCO 2019, P441.
3. Sands E, et al. ECCO 2019, DOP054.
4. Feagan BG, et al. ECCO 2019, DOP79.

Ustekinumab as maintenance therapy and with shortened interval

Ustekinumab was found to be safe and effective as maintenance therapy in ulcerative colitis and Crohn's disease [1].

Both ustekinumab 90 mg every 8 weeks (q8w) and every 12 weeks (q12w) subcutaneous achieved clinical remission and maintained clinical response, and was effective in achieving endoscopic healing and corticosteroid-free remission among patients with moderate-to-severe ulcerative colitis who were in clinical response with a single IV dose of ustekinumab. The safety results in ulcerative colitis patients were consistent with the known safety profile of ustekinumab in Crohn's disease.

These were the main results of the phase 3, double-blind, randomised withdrawal study UNIFI. Participants were 523 patients with moderate-to-severe active ulcerative colitis who failed conventional or biologic therapy (including anti-TNF and/or vedolizumab) and had clinical response 8 weeks after receiving a single IV ustekinumab induction dose. After 44 weeks, 43.8% and 38.4% of ustekinumab q8w and q12w patients, respectively, were in clinical remission vs 24% of patients in the placebo group ($P<0.001$ and $P=0.002$, respectively). Significantly greater proportions of ustekinumab q8w and q12w patients maintained clinical response through week 44 (68.0% and 71.0% vs

44.6%; P<0.001) and achieved endoscopic healing and corticosteroid-free clinical remission vs placebo patients. The proportions of patients with adverse events (AEs), serious AEs, infections, and serious infections in both ustekinumab groups were generally comparable with placebo (see Table).

Table: Summary of key safety findings through week 44

	Placebo subcutaneous[a]	Ustekinumab 90 mg subcutaneous q12w	Ustekinumab 90 mg subcutaneous q8w
Randomised patients	175	172	176
Average follow-up	42.3	41.8	42.2
Average exposure (no of administrations)	7.1	7.3	7.4
Patients who died	0	0	0
• Patients with 1 or more AEs	138 (78.9%)	119 (69.2%)	136 (77.3%)
• Serious AEs	17 (9.7%)	13 (7.6%)	15 (8.5%)
• Infections	81 (46.3%)	58 (33.7%)	86 (48.9%)
• Serious infections	4 (2.3%)	6 (3.5%)	3 (1.7%)
• AEs leading to discontinuation of study agent	20 (11.4%)	9 (5.2%)	5 (2.8%)
• Malignancies (excluding NMSC)	0	1 (0.6%)	1 (0.6%)

[a] Patients who had clinical response to ustekinumab IV induction dose and were randomised to placebo subcutaneous on entry of this maintenance study.
AE, adverse event; NMSC, nonmelanoma skin cancer; q8w every 8 weeks; q12w, every 12 weeks.

In the same UNIFI study, subjects with moderately to severely active ulcerative colitis receiving IV ustekinumab induction had higher rates of endoscopic healing, histological healing, and histo-endoscopic mucosal healing than those receiving placebo [2]. Approximately 10% of subjects who did not achieve clinical response 8 weeks after IV ustekinumab achieved histo-endoscopic mucosal healing following a second (subcutaneous) dose. Histological healing was associated with reductions in clinical and endoscopic disease activity as well as patient-reported symptoms.

Some Crohn's disease patients will partially respond to ustekinumab or will experience a secondary loss of response. These patients might benefit from shortening the interval between injections from 90 mg q8w to q4w. In a retrospective, multicentre cohort study, this treatment optimisation resulted in two-thirds of patients recapturing response (n=50/76) [3]. Clinical response was observed in 57% (n=43/69) after a median of 2.1 months. Colonic location, inflammatory behaviour, and duration of ustekinumab therapy before optimisation were associated with clinical response. After a median follow-up of 8.2 months, 47% (n=36/76) were still treated with ustekinumab; 26% (n=20/76) were in steroid-free clinical remission. Among the 29 patients with colonoscopy during follow-up, 10 had mucosal healing. At the end of follow-up, 35% (n=27/76) were hospitalised, and 22% (n=17/76) underwent surgery.

1. Sandborn WJ, et al. ECCO 2019, OP37.
2. Li K, et al. ECCO 2019, DOP71.
3. Fumery M, et al. ECCO 2019, OP24.

Tofacitinib: Results from the OCTAVE open-label studies

The ongoing, open-label, long-term extension (OLE) OCTAVE Open evaluates the efficacy and safety of tofacitinib in ulcerative colitis patients [1]. Participants have shown clinical response but not remission after 52 weeks of maintenance therapy in the OCTAVE Sustain study, and subsequently received tofacitinib 10 mg twice daily. Over 50% of patients who completed OCTAVE Sustain as clinical responders improved to remission within 2 months. Efficacy was observed regardless of prior anti-TNF failure status.

Of 82 patients, 38 (46.3%) had prior anti-TNF failure. Clinical response at 24 months was maintained by 69.5% of patients overall, and by 65.4% and 72.7% of patients with and without prior anti-TNF failure, respectively. By month 2, the proportion of patients who had improved to remission was 58.5%, 60.5%, and 56.8%, respectively. Remission rates at month 2 were 77.8% (n=14/18) for patients who had received placebo in OCTAVE Sustain, 57.1% (n=16/28) for patients who had received 5 mg twice daily, and 50.0% (n=18/36) for patients who had received 10 mg twice daily. No new safety concerns associated with tofacitinib emerged in the overall study population.

Also presented was an update of previous analyses of delayed responders to 16 weeks of tofacitinib 10 mg twice daily (8 weeks induction + 8 weeks OLE) [2]. Of 295 induction non-responders, 50.7% achieved clinical response. Of these 'delayed responders', 72.2%, 61.3%, and 54.3% showed clinical response at 12, 24, and 36 months, respectively. Mucosal healing was seen in 56.8%, 52.7%, and 51.4%, respectively. About 45% of patients were in remission at each time point after month 2. Treatment effects were generally similar regardless of prior anti-TNF failure status. Proportions of delayed responders who achieved clinical response, mucosal healing, and remission at 12 months were similar to responders to 8 weeks of treatment. Proportions of delayed responders with adverse and safety events of special interest were similar to 8-week clinical responders.

1. Chiorean M, et al. ECCO 2019, DOP41.
2. Rubin DT, et al. ECCO 2019, DOP43.

Safety of thiopurine + allopurinol vs thiopurine monotherapy

IBD patients on thiopurine and allopurinol did not have a statistically significant different risk of adverse outcomes (including initiation of a biologic) when compared with IBD patients exposed to thiopurine monotherapy. This conclusion is based on an analysis of a nationwide cohort of Danish IBD patients who had been prescribed thiopurine therapy between 1999 and 2014 [1].

In this period, 10,367 patients with IBD (5,484 Crohn's disease and 4,883 ulcerative colitis) were prescribed thiopurines; 217 of them used allopurinol co-therapy. The primary outcome was a composite of any adverse outcome or need for biological treatment: IBD-related hospitalisation, IBD-related surgery, biological therapy initiation, or death. In patients exposed to allopurinol co-therapy, there were 40 incident outcomes in 129 person-years (PY) (incidence rate 310.1 per 1,000 PY). In patients exposed to thiopurine monotherapy, 4,745 outcomes among 24,585 PY were observed (incidence rate 193.0 per 1,000 PY). The adjusted incidence rate ratio of an adverse outcome was not significantly different (1.26). The results did not differ when analysed in strata by IBD subtype (i.e. Crohn's disease or ulcerative colitis). Even though allopurinol co-therapy seems to improve clinical remission in IBD patients in previous studies, the Danish researchers concluded that their study does not suggest an association with subsequent clinical outcomes.

1. Thomsen SB, et al. ECCO 2019, DOP88.

Limited long-term effectiveness and safety of tacrolimus in ulcerative colitis

Tacrolimus is a calcineurin inhibitor commonly used for prophylaxis of rejection in renal and liver transplantation. Efficacy and safety of tacrolimus in ulcerative colitis were evaluated in a retrospective, multicentre study performed in Spain, in which 58 patients received tacrolimus between 1999 and 2018 [1]. The most common indications for tacrolimus were steroid-dependency (55%) and steroid-refractory disease (29%). The median clinical follow-up was 25 months.

Tacrolimus offered a clinical benefit in medically refractory ulcerative colitis in the short-term, but its long-term effectiveness and safety was found to have important limitations. After 3 months, partial Mayo score had decreased significantly (mean 1.6, P=0.0001), with 36% of patients having partial response and 24% being in clinical remission. One third of patients (35%) suffered adverse events related to the drug (40% tremor, 20% asthenia), leading to discontinuation in 35%. The drug was stopped in 81% of patients after a median of 14 months, with 47% requiring a new immunomodulator, 28% hospitalisation, and 33% colectomy thereafter.

1. Rodriguez-Lago I, et al. ECCO 2019, DOP44.

Complementary and Alternative Medicine

Topical review

At the ECCO 2019 meeting, a topical review focused on the most commonly used complementary and psychotherapy interventions in inflammatory bowel disease (IBD). The two speakers, Dr Joana Torres (New University of Lisbon, Portugal) and Prof. Stephan Vavricka (Gastroenterology and Hepatology Center, Zurich, Switzerland), noted a lack of rigorously conducted trials in this field, which is why further research is needed before any solid recommendations can be made.

Prof. Vavricka said 20-60% of IBD patients use some form of complementary and alternative medicine (CAM) [1]. A topical review was performed aiming to inform physicians and to provide some evidence to guide an informed

discussion with their patients on CAM. There were three working groups:

- biologically based practices, such as herbs, cannabis, probiotics;
- manipulative and body-based interventions; and
- mind-body medicine and psychotherapeutic interventions.

Biologically based practices

Quite a few studies (even randomised trials) are available on the induction and maintenance of remission in both ulcerative colitis and Crohn's disease. Although the use of cannabis may be associated with a reduction of some symptoms of IBD, there is no firm evidence to show that it positively alters the course of the disease. As a complementary therapy to 5-ASA, curcumin may be effective in inducing remission in mildly to moderately active ulcerative colitis. Curcumin, psyllium, and an herbal preparation consisting of myrrh, chamomile, and coffee charcoal may be effective as complementary therapy in ulcerative colitis.

Vitamin D may play an important role in the pathogenesis of IBD. Deficiency of vitamin D often occurs in IBD patients. Prof. Vavricka: "There is insufficient evidence, however, to support the use of any vitamins or minerals to induce or maintain remission in ulcerative colitis or Crohn's disease."

Dietary fibre supplements, such as prebiotics (fructo-oligosaccharides) and short-chain fatty acids, psyllium, and germinated barley, may stimulate the growth of selected beneficial microbial species (i.e. *Bifidobacteria, Faecalibacterium prausnitzli*). There is insufficient evidence to support the use of dietary supplements or specific diets to induce or maintain remission in Crohn's disease or ulcerative colitis. However, future research should focus on diet as a complementary therapy.

Fish oil is known to reduce the production of certain pro-inflammatory markers, such as IL-1, IL-6 and TNF. Omega-3 fatty acids have shown a marginal benefit vs placebo in maintaining remission in Crohn's disease. However, study quality and heterogeneity of trials limit the value of these findings.

Body-based interventions

Some studies have suggested that acupuncture could improve inflammation, symptoms, and quality of life, but these studies mostly lack sufficient quality. According to Dr Torres the same may be said of moxibustion, i.e. the burning dried mugwort (muxa) directly or indirectly on acupoints to generate warmth stimulation. "Therefore, we conclude there is insufficient evidence to support the use of acupuncture or moxibustion, either as monotherapy or in combination, for the treatment of active ulcerative colitis or Crohn's disease."

Further, exercise may protect from IBD. A prospective study from the Nurses' Health Study (NHS) cohorts found that the risk of Crohn's disease among women in the highest quintile of physical activity was 0.64 compared with women in the lowest quintile [2]. Active women with at least 27 metabolic equivalent task hours per week of physical activity had a 44% lower risk of Crohn's disease compared with sedentary women with <3 metabolic equivalent of task-hours per week. Physical activity was not associated with risk of ulcerative colitis (P for trend 0.46). Several studies have shown the safety of mild-to-moderate exercise programmes in IBD. No detrimental effects on disease activity were found. Exercise programs are associated with a higher quality of life. Overall, exercise can have beneficial effects on overall health, physical wellbeing, perceived stress, and quality of life of IBD patients. There is promising, albeit limited, evidence of the role of exercise both in protecting from IBD and in disease management.

Psychotherapy and mind-body interventions

Dr Torres stressed that there are high rates of functional gastro-intestinal disorders, anxiety, and depression, especially in patients with active disease. Also, some evidence suggests that stress is associated with a higher relapse risk. Cognitive behavioural therapy has shown no effect on disease activity, but positive effects on quality of life have been reported. Outcomes on anxiety and depressions are mixed. Results of two randomised controlled trials of yoga indicate no effect on inflammatory markers but improvements in quality of life, anxiety and abdominal pain. Meditation and relaxation may improve quality of life and possibly decrease inflammatory activity in IBD. Evidence of the effect of mindfulness-based interventions on disease activity are limited. Gut-directed hypnotherapy is efficacious in functional gastro-intestinal disorders, but evidence of any effect on IBD is limited.

1. Torres J and Vavricka S. ECCO 2019.
2. Khalili H, et al. BMJ. 2013 Nov 14;347:f6633. doi:10.1136/bmj.f6633.

Complementary and alternative medicine associated with chronic fatigue and lower QoL

One third of the inflammatory bowel disease (IBD) patients in a Norwegian cohort reported use of complementary and alternative medicine (CAM) 20 years after diagnosis. CAM use was associated with female gender, younger age, disease activity, chronic fatigue, and lower health-related quality of life (HRQOL) scores in 3 out of 8 dimensions of the Short-Form 36 (SF-36) [1].

From January 1990 to December 1993, all newly diagnosed patients with IBD from a well-defined area in South Eastern Norway were included in the Inflammatory Bowel South-Eastern Norway (IBSEN) study. The 20-year follow-up was conducted between 2011 and 2014. The Fatigue Questionnaire, the Short-Form 36 (SF-36), and the Hospital Anxiety and Depression Scale (HADS) were used to measure chronic fatigue, HRQOL, and anxiety and depression, respectively. Additionally, patients answered a questionnaire about CAM use.

Of 599 patients invited, 470 (ulcerative colitis 314, Crohn's disease 156) participated in the study. Of these, 439 produced evaluable questionnaires. The use of CAM for their IBD was reported by 28% (n=122/439). CAM users were more likely to be women than men (60% vs 40%; P=0.02) and were younger than non-users (mean 49 vs 56 years; P<0.001). A significantly higher proportion of CAM users reported chronic fatigue (30% vs 20%; P=0.02). CAM users had significantly lower SF-36 scores in the following 3 dimensions: Vitality (51 vs 57; P≤0.01), Physical functioning (85 vs 89; P=0.04), and Social functioning (77 vs 84; P=0.01). There were no differences in anxiety and depression scores.

1. Opheim R, et al. ECCO 2019, P250.

Crohn's disease exclusion diet + partial enteral nutrition in paediatric Crohn's disease

In a multicentre, randomised, controlled trial, Crohn's disease exclusion diet (CDED) + partial enteral nutrition (PEN) showed superior tolerance and sustained remission compared with exclusive enteral nutrition (EEN) in children with mild-to-moderate luminal Crohn's disease [1]. Thus, it could be used as first-line therapy for children with luminal mild-to-moderate active Crohn's disease.

Dr Arie Levine (Mount Saint Vincent University, Canada) explained that emerging data suggests a strong environmental component in the pathogenesis of Crohn's disease, and an important role of the microbiota. He also explained that if the dietary factors that drive inflammation could be identified and removed from the diet, inflammation could be reduced and remission induced without requiring EEN by using an exclusion diet with whole foods. This was the study's incentive to compare CDED + PEN with EEN in a 12-week prospective, international trial in 78 children from 13 sites aged 6-18 years with a paediatric Crohn's disease activity index (PCDAI) ≥10, and elevated inflammatory markers. The combination therapy aimed to reduce exposure to dietary components hypothesised to negatively affect the microbiome, intestinal barrier, and innate immunity. The primary endpoint was tolerance to diet; secondary endpoints included week 6 intention to treat (ITT) remission defined by PCDAI ≤10 after 6 weeks, and corticosteroid free ITT-sustained remission after 12 weeks.

In 74 analysed patients, tolerance was significantly better in the CDED + PEN group: 97.5% vs 73.7% (P=0.003). Poor compliance was similar in both groups: 17.5% vs 23.5% (P=0.52). Dr Levine found the difference in remission surprising:

- week 6 ITT corticosteroid-free remission (PCDAI ≤10) occurred in 80% in the CDED group vs 73.5% in the EEN group (P=0.51);
- more strictly defined remission (PCDAI <10) was seen in 75% vs 59% (P=0.38); and
- sustained corticosteroid-free free remission at week 12 (PCDAI ≤10) was 70% vs 41.2% (P=0.01).

"These are convincing data for induction of remission and for sustaining remission with CDED + PEN in mild-to-moderate active Crohn's disease in children," Dr Levine said. "They also convincingly show that diet reduces inflammation and that re-exposure to diet increases inflammation and reduced sustained remission." The outcomes support a mechanism whereby inflammation is induced by *Proteobacteria*-led dysbiosis, remission by a decline in *Proteobacteria* with expansion of *Firmicutes*, and loss of remission by rapid return of dysbiosis with exposure of food. "The outcomes support using CDED + PEN for 12 weeks as a first-line therapy to replace EEN in mild-to-moderate active Crohn's disease in children."

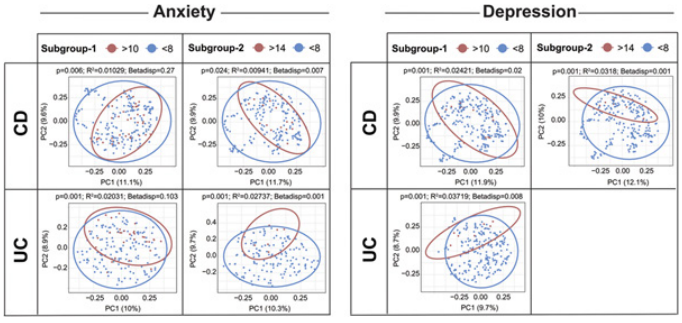
1. Van Limbergen J, et al. ECCO 2019, OP05.

Microbial composition and psychological wellbeing

The gut-brain axis was revisited from an interesting angle: Dr Luc Biedermann (University Hospital Zurich, Switzerland) and colleagues looked at a potential interplay between microbial composition and validated psychological outcome measurements in inflammatory bowel disease (IBD) patients [1]. They found significant alterations in the intestinal mucosa-associated microbiome composition in IBD patients in remission in relation to psychological wellbeing and quality of life.

Study participants were 171 patients with available microbial sampling who were in clinical remission, to exclude a potential impact of disease activity. Patients with higher perceived stress had significantly lower alpha diversity, whereas patients with high vs low levels of anxiety and depressive symptoms showed no substantial differences in alpha diversity. In IBD patients with vs without depression or anxiety, beta diversity was significantly different (as shown in the Figure). Looking at specific operational taxonomic unit (OTUs), several significant alterations across groups were seen. These included significant increases in represents of *Proteobacteria*, such as *Desulfovibrio* (P=0.001), in ulcerative colitis patients, as well as decreases in numerous genus of *Firmicutes*, such as *Lachnospiraceae* (P<0.001), in Crohn's disease and ulcerative colitis patients with depression; and decreases in *Lactobacillales* (*Streptopcoccaceae*) in Crohn's disease patients with anxiety (P<0.001).

Figure: Beta diversity in IBD patients with vs without depression or anxiety [1]



Principal component analysis of microbial beta diversity according to severity (subgroup 1 = moderately increased, subgroup 2 = severe vs normal anxiety and depression) of psychological alteration (no ulcerative colitis patients with severe depression in this sample). CD, Crohn's disease; UC, ulcerative colitis.

Dr Biedermann noted that further studies are warranted to gain more insight into the direction of the link between microbial composition and psychological wellbeing, and to investigate whether intestinal inflammation subsequent to microbial alterations or microbial metabolites itself may impair psychological wellbeing.

1. Humbel F, et al. ECCO 2019, OP06.

Glycans as novel immunomodulators in inflammatory bowel disease

Portuguese scientists assessed whether glycosylation of T cells is a previously uncovered factor that tips the balance between homeostasis and intestinal inflammation. They proposed glycans as novel immunomodulators in inflammatory bowel disease (IBD), disclosing a promising predictive glycobiomarker associated with therapy response [1].

Ulcerative colitis patients exhibit a deficiency in branched glycosylation in intestinal T cells, which is reflective of disease severity. The Portuguese group tested the impact of specific glycans as immunomodulatory agents *in vitro, ex vivo,* and in preclinical mouse models of IBD, after which they performed clinical validation in human samples. Metabolic supplementation of *ex vivo* mucosal T cells from active ulcerative colitis patients with GlcNAc resulted in enhancement of branched N-glycosylation in the T cell receptor (TCR), leading to suppression of T cell growth, inhibition of the Th1/Th17 immune response, and controlled T cell activity. Mouse models displaying a deficiency in the branched N-glycosylation pathway (MGAT5−/−, MGAT5+/−) exhibited increased susceptibility to severe forms of colitis and early-onset disease. The treatment of these mice with glycan N-acetylglucosamine (GlcNAc) significantly reduced disease severity and suppressed disease progression; this was due to a controlled T cell-mediated immune response at the intestinal mucosa. Furthermore, the levels of expression of branched N-glycans analysed in colonic biopsies of ulcerative colitis patients close to diagnosis were found to predict failure to standard therapy.

1. Dias A. ECCO 2019, OP04.

Remission

Early remission of Crohn's disease prevents progression

Deep remission is often the goal in treating inflammatory bowel disease (IBD), now that treatment has significantly improved in the past few years due to new targeted biologic therapies, the optimisation of older therapies, and a better understanding of the pathogenesis. But what is the impact of achieving endoscopic and deep remission on the natural course of IBD in the long term? Study results have shed more light on this important issue, most notably the follow-up data of the CALM study.

A retrospective analysis of medical records of patients with follow-up data since the end of CALM showed that patients with early Crohn's disease (CD) who achieve endoscopic or deep remission after 1 year of intensive treatment are less likely to have disease progression over a median of 3 years [1]. The results were presented by Dr Thierry Yzet (Amiens University Hospital, France). Participants (n=122) from 31 centres were stratified by outcomes in CALM at 1 year:

- clinical remission (Crohn's disease activity index, CDAI <150);
- endoscopic remission (Crohn's disease endoscopic index of severity, CDEIS <4 with no deep ulcerations); and
- deep remission (CDAI <150, CDEIS <4 with no deep ulcerations, and no steroids for ≥8 weeks).

The primary outcome was a composite of major adverse outcomes reflecting CD progression: new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalisation, or CD surgery since the end of CALM. Median follow-up time from the end of CALM was 3.02 years. Fifty per cent of participants were randomised to the tight control arm. During follow-up, 34 patients (27.9%) had a major adverse outcome. Patients in clinical remission at 1 year did not have significantly lower rates of the composite endpoint (log-rank P=0.15). Patients in endoscopic and deep remission at the end of CALM were significantly less likely to have a major adverse event over time.

After adjusting for age, disease duration, prior surgery, prior stricture, and randomisation arm, endoscopic remission (aHR 0.44, P=0.038) and deep remission (aHR 0.25, P=0.01) were significantly associated with lower risk of major adverse events. Dr Yzet concluded: "Early CD patients who achieve endoscopic and deep remission at 1 year, had a 56% and a 75% decreased risk, respectively, of disease complications over a median of 3 years" (Figure 1 and 2). "Reaching the targets of endoscopic and deep remission early in the course of CD can result in long-term disease modification."

Figure 1: Kaplan-Meier estimates of CD disease progression based on endoscopic remission at 1 year [1]

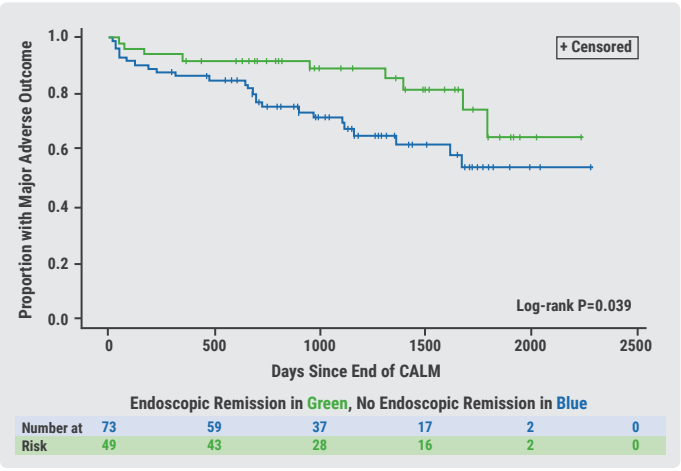
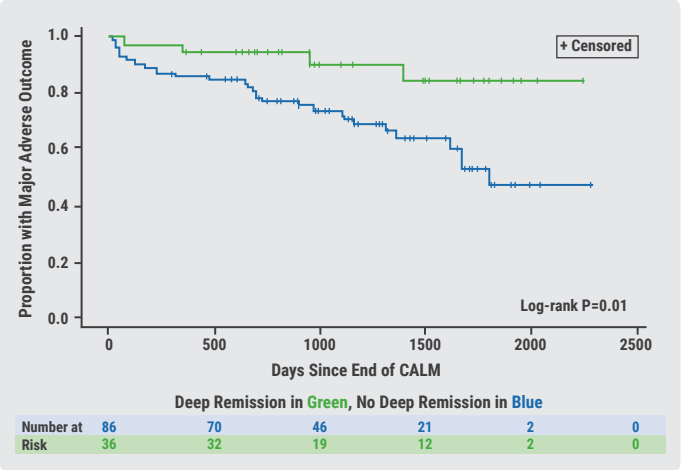


Figure 2: Kaplan-Meier estimates of CD disease progression based on deep remission at 1 year



1. Yzet T, et al. ECCO 2019, OP35.

Histological remission predicts relapse-free survival in ulcerative colitis

Histological grade is an important prognostic marker in ulcerative colitis patients in clinical and endoscopic remission. Histological remission independently predicts significantly longer relapse-free survival and, thus, may be a superior therapeutic target compared with endoscopic remission.

These were the main conclusions drawn from a single-centre study that aimed to assess histological activity using the validated Nancy histological activity score as a predictor of future relapse [1]. Enrolled were 74 ulcerative colitis patients in both clinical and endoscopic remission attending a tertiary centre in Canberra, Australia, between 2015 and 2018. Clinical remission was defined as partial Mayo score (MSp) <2, and endoscopic remission was defined as Mayo Endoscopic Subscore (MES) ≤1. Median follow-up was 42 months, the median relapse free period 30 months.

Patients with MES 0 (P=0.02) and histological remission (P≤0.0001) had a significantly longer relapse free survival. Multivariate analysis showed that histological activity was the only independent risk factor of future clinical relapse (HR 4.36, 95% CI 1.68-11.27; P=0.002). The authors added that long-term prospective studies will need to determine whether histological remission improves clinical and patient-reported outcomes.

1. Wang H, et al. ECCO 2019, DOP68.

Proactive adalimumab trough measurements

In biological-naïve children with luminal Crohn's disease who responded to adalimumab induction, repeated proactive trough measurements plus tight control resulted in higher corticosteroid-free sustained remission rates than reactive trough measurements and tight control.

These were the main outcomes of the first-ever paediatric randomised controlled trial to determine whether proactive therapeutic drug monitoring to maintain serum levels of adalimumab above 5 µg/ml is associated with higher rates of clinical remission than the reactive approach, in which drug measurement is only done when clinically indicated [1]. First author Dr Amit Assa (Schneider Children's Hospital, Israel) received the ECCO 2019 award for best researcher-initiated study for this abstract.

A total of 80 children aged 6-18 years who responded to adalimumab induction were randomised to a proactive or a reactive group. In the proactive group, trough concentrations were measured at week 4, 8, and every 8 weeks thereafter until week 72. Dose or intervals were adjusted to maintain levels >5 µg/ml. In the reactive group, physicians were informed of the trough levels only when clinically indicated, adjusting dose/intervals based upon the levels.

The primary endpoint was sustained corticosteroid-free clinical remission from week 8 to 72. Significantly more children in the proactive group met this endpoint: 34 (87%) vs 21 (49%) (P<0.001). At week 72, corticosteroid-free clinical remission on adalimumab was reached by 32 (82%) and 20 (48%) in the proactive and reactive group, respectively (P<0.001). Clinical indices, C-reactive protein, and faecal calprotectin correlated with adalimumab trough concentrations. Faecal calprotectin reduction rate was significantly higher in the proactive group. There were more patients undergoing dose/interval adjustments in the proactive group: 32 (82%) vs 18 (44%) (P<0.001).

Dr Assa concluded that children with Crohn's disease treated with adalimumab may benefit from therapeutic drug monitoring, even though severe exacerbations and drug discontinuation rates were similar. He added: "Since adalimumab intensification is the rule rather than the exception, this calls for early optimisation of trough concentrations."

1. Assa A, et al. ECCO 2019, OP18.

Relapse after withdrawal of thiopurines

Since long-term treatment with thiopurines is associated with an increased risk of opportunistic infection, lymphoma and other malignancies, treatment withdrawal should be considered in patients who are in deep remission.

The Royal Bournemouth Hospital in the United Kingdom looked at the consequences of discontinuing thiopurine and found that 28 of 72 patients (38.8%) relapsed: 17 patients with ulcerative colitis (60.7%) and 11 with Crohn's disease (39.3%) [1]. Of these, 79.4% relapsed within 3 years. Reassuringly, 71.5% achieved remission on re-starting AZA/methotrexate/mesalazine. Interestingly, 3 of their patients were identified to be in remission with faecal calprotectin but had mild inflammation on endoscopy; these 3 patients subsequently relapsed. This may suggest the need to establish remission endoscopically rather than using faecal calprotectin alone.

1. Radhakrishnan P, et al. ECCO 2019, P667.

Observational Studies

The costs and benefits of biologicals

Expenses linked to prescription of biologicals to inflammatory bowel disease (IBD) patients have increased sharply over the past few years. But what effect do they have on total costs? To what extent are these expenses paralleled by decreasing direct healthcare-related costs and decreasing costs of standard treatments, surgery, and hospitalisation? Two observational studies give more insight in direct and indirect costs of IBD.

Data from a European cohort (Epi-IBD) of unselected IBD patients indicated a cost-saving effect of biological medications, despite their high acquisition costs [1]. Over a period of 5 years, overall direct healthcare expenses decreased in parallel with remarkably increasing expenditure on biologics, particularly in Crohn's disease (CD) patients, and decreasing expenditure on standard medical treatments, surgery, and hospitalisation.

This is the first-ever prospective long-term analysis of healthcare costs in European IBD-patients in the era of biological treatments in Europe. Dr Johan Burisch (Frederiksberg Hospital, Denmark) received the Young ECCO (Y-ECCO) award for this abstract. The analysis was based on a population-based inception cohort of IBD patients from 31 centres in 20 European countries in 2010. Costs were specified for each centre. Of the 1,362 included IBD patients, 52% had UC, 37% CD, and 11% unclassified IBD.

Mean total expenditure per patient-year (PY) was highest in the first year in both Western and Eastern Europe, and then decreased. For CD patients, mean total expenditure was €5,579 in Y1 and €1,669 in Y5. For UC patients, it amounted to €3,612 and €674, respectively (see also Tables 1 and 2). The proportion spent on biologicals was lowest in the first year (11% and 2%, respectively) and rose to 55% and 25% in Y5. Expenditure on biological therapy increased in both Western Europe (PY1 €338, PY5 €516) and Eastern Europe (PY1 €31, PY5 €292). In both regions, this was paralleled by a steady decrease of costs of non-biological treatment, hospitalisation, and surgery. In a regression analysis, patients with worse disease phenotype as well as age ≥40 years generated higher costs. The overall outlay on biological therapy, expressed as a percentage of total expenditure, varied by age group: ≥40 years, 29%; 41-60 years, 21%; and ≥61 years, 11%. Dr Burisch added that expenditure on biologicals varied greatly per country, due to factors such as pricing and reimbursement.

Table 1: Mean total expenditure (€/patient) as well as proportion of expenditure spent on different categories of direct costs in patients with Crohn's disease [1]

	PY1	PY2	PY3	PY4	PY5
Total expenditure	€ 5579	€ 1820	€ 1714	€ 1907	€ 1669
Biological therapy (%)	11	46	51	48	55
Other IBD-related medication (%)	5	13	11	11	12
Hospitalisation (%)	20	14	11	11	6
Diagnostic procedures (%)	34	17	11	12	10
Surgery (%)	30	9	16	18	17

IBD, inflammatory bowel disease; PY, patient year

Table 2: Mean total expenditure (€/patient) as well as proportion of expenditure spent on different categories of direct costs in patients with ulcerative colitis [1]

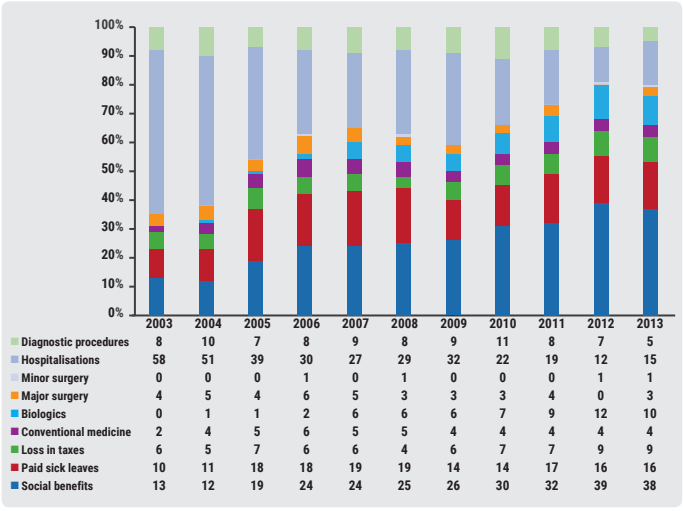
	PY1	PY2	PY3	PY4	PY5
Total expenditure	€ 3612	€ 1421	€ 810	€ 983	€ 674
Biological therapy (%)	2	7	20	19	25
Other IBD-related medication (%)	15	23	29	21	26
Hospitalisation (%)	35	29	21	33	17
Diagnostic procedures (%)	38	20	20	19	19
Surgery (%)	10	21	10	8	13

IBD, inflammatory bowel disease; PY, patient year

In a prospective Danish population-based cohort, the combined direct and indirect cost of IBD were assessed over a period of 10 years [2]. Direct costs for IBD remained high, but indirect costs did not surpass those of the control population. Total costs were mainly driven by hospitalisation; yet, over time, indirect costs accounted for a higher percentage, although they also decreased over the years. All incident patients (n=513) diagnosed between 2003 and 2004 in a well-defined area with CD (n=213) or UC (n=300) were followed prospectively until 2015. Direct and indirect costs were compared with a control population matched by age, sex, and municipality.

No significant differences were found in indirect costs between CD, UC, and the control population regarding paid sick leave, unemployment benefits, or loss of tax income. For CD patients, all direct costs (except for 5-ASA) were significantly higher than for UC patients. No differences were observed in diagnostic expenses (see Figure 1 for the distribution of expenses). Subgroup analyses only revealed significant increased direct expenses over time in patients with extensive colitis (proctitis: €2,273, left-sided: €3,606, extensive: €4,093, P<0.001). No variables were significantly associated with increased total costs in CD or UC patients.

Figure: Distribution of costs per year in patients with inflammatory bowel disease [2]



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Diagnostic procedures	8	10	7	8	9	8	9	11	8	7	5
Hospitalisations	58	51	39	30	27	29	32	22	19	12	15
Minor surgery	0	0	0	1	0	1	0	0	0	1	1
Major surgery	4	5	4	6	5	3	3	3	4	0	3
Biologics	0	1	1	2	6	6	6	7	9	12	10
Conventional medicine	2	4	5	6	5	5	4	4	4	4	4
Loss in taxes	6	5	7	6	6	4	6	7	7	9	9
Paid sick leaves	10	11	18	18	19	19	14	14	17	16	16
Social benefits	13	12	19	24	24	25	26	30	32	39	38

Conventional medicine: 5-aminosalicylic acid, topical steroids, corticosteroids, and immunosuppressants.

1. Burisch J, et al. ECCO 2019, OP015.
2. Lo B, et al. ECCO 2019, DOP82.

Efficacy and safety of biosimilars

Data are emerging on the safety and efficacy of the first biosimilars of infliximab. Results from an interim analysis of the infliximab biosimilar CT-P13 in a real-world setting were presented [1]. Also presented were the first worldwide data on the use of the infliximab biosimilar SB2 in inflammatory bowel disease (IBD) [2].

The interim analysis of preliminary data from the CONNECT-IBD study showed that safety of CT-P13 is consistent with the known safety profile of infliximab; no new safety information was identified that warrants a change in the benefit-risk profile of CT-P13 [1]. CONNECT-IBD is an ongoing, non-interventional, observational cohort study evaluating CT-P13 in the context of usual care with the infliximab reference product in the treatment of Crohn's disease (CD) and ulcerative colitis (UC) patients in a real-world setting.

Patients were recruited at 150 academic and community sites in 13 European countries. Adult CD or UC patients prescribed with CT-P13 or EU-sourced infliximab reference product at the investigator's discretion were eligible. This descriptive analysis included 1,957 patients (CT-P13, n=1,825; Switched, n=132). Of these patients, 1,264 had CD and 692 had UC. In total, 626 treatment-emergent adverse events (AEs) were reported in 438 (22.4%) patients, equally distributed in the CT-P13 (22.2%) and Switched (25.0%) groups. Incidences of treatment-emergent AEs, serious treatment-emergent AEs (12.1% vs 12.1%) and treatment-emergent AEs leading to discontinuation of study drug (8.1% vs 6.8%) were balanced between CT-P13 and Switched groups, respectively. The higher percentage of Switched (2.3%) vs CT-P13 (0.9%) patients withdrawing due to AEs was likely driven by the smaller number of patients in the Switched group. Most patients reported treatment-emergent AEs of mild-to-moderate intensity (overall: mild, 7.3%; moderate, 9.2%; severe, 5.8%).

Preliminary data from the SPOSIB SB2 study on the use of SB2 showed that efficacy and safety seem to be similar overall to those reported for infliximab originator and infliximab biosimilar CT-P13 [2]. SPOSIB SB2 is a multicentre, observational, prospective study of the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD). All consecutive CD and UC patients starting SB2 from March 2018 to September 2019 are eligible. The primary endpoint is safety. Presented during the congress were the results from the first 6 months of the study, which included 77 patients (CD 50.6%, UC 49.4%). Most patients (n=46; 59.7%) were anti-TNFs naïve, while 66 patients (85.7%) were not previously exposed to infliximab, 8 patients (10.4%) switched from infliximab originator to SB2, and 3 (3.9%) switched from infliximab biosimilar CT-P13 to SB2. The mean follow-up was 2.2 ± 1.7 months. Serious AEs occurred in 7 patients (9.1%); 6 of these led to withdrawal of the drug. In detail, 3 infusion reactions were reported, 3 arthritic flares/arthralgias, and 1 case of flu-like syndrome.

The efficacy of SB2 was evaluated in 35 patients who completed at least 8 weeks of follow-up. Seventeen patients (48.6%) had steroid-free remission after 8 weeks, 8 (22.8%) achieved a partial response, while 10 had no

response (28.6%). Among the 25 patients with steroid-free remission or response at week 8, the efficacy rates were 96.6%, 89.1%, and 72.8% after 12, 16, and 20 weeks of therapy, respectively.

1. Bokemeyer B, et al. ECCO 2019, P590.
2. Macaluso FS, et al. ECCO 2019, P737.

Infliximab retreatment in luminal Crohn's disease

After discontinuation of infliximab due to loss of response or intolerance, infliximab retreatment is safe and efficient in more than one third of Crohn's disease (CD) patients regardless of the reason of prior discontinuation. This was concluded from a prospective, multicentre, observational cohort study, which included 96 patients with active luminal CD who resumed infliximab therapy after at least 6 months of discontinuation [1].

At baseline, patients had clinically (Crohn's Disease Activity Index [CDAI]>150) and objectively active CD. The reintroduction schedule included 3 infliximab infusions at weeks 0, 4, and 8, after a systematic premedication. Maintenance treatment was administered every 8 weeks. At week 26, 34 patients (35%) reached the primary endpoint of efficacy, defined as a CDAI <150 in the absence of infliximab discontinuation or use of corticosteroid therapy, surgery, or another biologic. No significant difference was observed in rates of clinical remission in patients with initial secondary loss of response (38%) and those with infliximab intolerance (33%) (P=0.9). A total of 37 patients (36%) had an intolerance reaction to retreatment after an average of 3 infliximab infusions, requiring drug discontinuation for 31 (30%) patients. Optimisation of infliximab treatment by increasing doses and/or frequency of infusions was necessary in 45 patients (47%) during the 12-month follow-up period. Neither the presence of anti-drug antibodies at baseline nor infliximab trough level at week 8 were predictive of infliximab retreatment failure.

1. Boschetti G, et al. ECCO 2019, P714.

IBD risk of treatment with IL-17 antagonists

Trials in psoriasis, psoriatic arthritis, and ankylosing spondylitis have reported cases of inflammatory bowel disease (IBD) during anti-IL-17 treatment. However, a recent systematic review and meta-analysis did not find an increased risk for development of IBD in patients treated with IL-17 antagonists [1].

Dr Wolfgang Eigner (deceased 10 March 2019, in memoriam) and colleagues (Medical University of Vienna, Austria) conducted a systematic review and meta-analysis evaluating IBD risk during treatment with secukinumab, ixekizumab, or brodalumab in patients with psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis. Included were 66 published and unpublished studies between 2010 and 2018. Data of 14,390 patients exposed to anti-IL-17 treatment was evaluated during induction treatment; 11 incident cases of IBD (worst-case scenario) were identified. In the 19,380 patients who analysed for the entire treatment period, 33 new cases were diagnosed (worst-case scenario). In the meta-analysis, a pooled incidence rate of 0 events for the worst-case scenario and for all sub-analyses was found. Prospective trials evaluating this possible risk are therefore warranted, according to the researchers.

1. Eigner W, et al. ECCO 2019, DOP86.

Significant differences in drug survival in both CD and UC

Interview with
Prof. Bjørn Moum,
on the results of two observational studies from Norway

At the ECCO 2019 meeting, two posters were presented on studies concerning drug survival of biologics in a national cohort of Norwegian IBD patients; one study included patients with Crohn's disease (CD), the other patients with ulcerative colitis (UC) [1,2]. In both first- and second-line treatment, drug survival of biologics differed significantly. Study coordinator Prof. Bjørn Moum (Oslo University Hospital, Norway) explains the results and the value of these data.

First of all, why is drug survival an important issue?

"There is a lack of real-world data on the use of biologics in IBD patients. Discontinuation of a drug may be caused by diminishing effectiveness or by adverse events (AEs). It is clear that an anaphylactic reaction to TNF-alpha, even though it rarely occurs, will cause the patient to discontinue this treatment. We know much less about the impact of other AEs, such as skin conditions or arthritis. What makes these AEs difficult to evaluate, is that they may be extra-intestinal manifestations of IBD itself. It can be hard to distinguish between AEs caused by a treatment and those caused by the disease itself. Be that as it may, biologics, especially TNF-alpha inhibitors (TNFi), are often discontinued due to perceived AEs or ineffectiveness. In both cases, the problem is often immunogenicity: the formation of anti-drug antibodies. It is important to know this and take action; it is also important to know if TNFi differ in their immunogenicity rates."

Which biologics did you include in your study and why?

"In both studies, data were collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database. We included those TNFi and other biologic treatments that are available in Norway. The choice in our country is limited due to the principle of tendering. This is a formal procedure using competitive bidding to choose preferred treatment(s). As first-line therapies, the TNFi adalimumab (ADA) and infliximab biosimilar CTP-13 (IFX) were most frequently used for both CD and UC patients; golimumab (GOL) was sometimes prescribed in UC patients, but much less. In Norway, vedolizumab (VDZ) is used as second-line treatment only, where it is prescribed more and more frequently. Due to the tendering process, this seems to be the only extra second-line option until at least 2020. So, if a TNFi needs to be discontinued, there are two options in Norway: switch to another TNFi or switch to vedolizumab. I personally prefer not to switch to a second TNFi, but am aware that different opinions on this matter exist."

How would you summarise the main findings? [see box]

"In both the CD and the UC cohort, we found significant differences in drug survival in both first-and second-line treatment. In CD, VDZ survival was significantly higher than ADA and IFX as second-line treatments. But perhaps the most interesting finding was the significantly higher survival of IFX vs ADA in first-line treatment. In UC, survival of both IFX and GOL was significantly higher than of ADA in first-line treatment. ADA survival also differed significantly from GOL and VDZ survival in second-line treatment."

Main results of the studies in CD and UC patients

In the CD study [1], a total of 2,444 patients were included. After 3 years, the survival rate of first-line biologics for CD patients was significantly higher for IFX than for ADA: 50.3% and 40.5%, respectively (P<0.001). For second-line treatment, the survival rates were 42.4% for IFX, 42.8% for ADA, and 69.8% for VDZ. Compared with ADA and IFX, VDZ survival was significantly different (P<0.001). Six months before or after starting treatment, 72.4% of IFX and 56.6% of ADA patients received an immunomodulator (P<0.001).

The UC study included 2,113 patients [2]. After 3 years, the survival rate of first-line biologics for UC patients was 42.7% for IFX, 28.7% for ADA, and 33.7% for GOL. The difference between ADA and both IFX and GOL survival was significant (P<0.001). For second-line treatment, the survival rates were 35.9%, 32.3%, and 43.7%, respectively, and 58.8% for VDZ. ADA survival differed significantly from GOL and VDZ survival (P<0.01 and P<0.001). VDZ survival was also significantly different from IFX (P<0.001). Six months before or after starting treatment, 65.1% (IFX), 57.4% (ADA), and 49.5% (GOL) of patients received an immunomodulator (GOL vs IFX P<0.001, and P>0.05 for the other comparisons).

How would you explain these differences?

"That is the next step in our study; we are still working on this. We have already analysed some factors that could explain it. One possible explanation of the differences in survival in CD is the higher immunomodulator use in the IFX groups, which could account for the lower rates of immunogenicity. In ADA users, adherence could also be a matter of concern. For the administration of IFX and biologicals patients come to the hospital; if they don't show up, we will call them. ADA adherence is harder to check because patients administer it at home. This is why CD patients with the most severe disease will receive IFX; we can better monitor adherence and control the dosage, which sometimes needs to be increased. Apart from this, choosing between the two TNFi is also a question of economy. Since 2015, Norwegian IBD patients have only been prescribed IFX as first-line treatment, because in that year the biosimilar became available. As a consequence, almost all patients on ADA in our cohorts started this treatment before 2015.

In the UC cohort, the same two factors explain the differences in drug survival: immunogenicity and compliance. I do not have an explanation for the difference between IFX and GOL in favour of GOL. I do not think it has to do with compliance. Considering we had only 93 GOL users, it may actually have been a chance finding."

What would you say is the overall robustness of these findings, and how do they extrapolate to other countries?

"For ADA, IFX, and VDZ they are quite robust in both CD and UC, at least the first year or year and a half. After that, less so, because numerous patients are beginning to drop out. Of course, the choice of drugs prescribed elsewhere in Europe as first- and second-line treatment of IBD may vary a great deal from one country to the next. Our data mirrors the limited choice in Norway concerning first-line treatment as a result of the tenders. We are currently conducting a similar study together with Denmark, Sweden, and Finland, in order to expand our results.

I must say, a recently published Dutch study on drug survival did not find significant differences like we did [3]. However, in their study more patients were on steroids and more were hospitalised when treated with adalimumab.

Is (permanent) discontinuation of a drug always undesirable? A single-centre retrospective analysis, conducted at an Irish hospital, found low relapse rates among patients with CD and UC who discontinued treatment after achieving sustained remission [4].

"We do not know that yet. There are four studies ongoing to evaluate this. One of these is BIOSTOP, a prospective, open randomised study with parallel groups to compare the outcomes of discontinuing vs continuing TNFi in Norwegian UC patients who are in remission. Hopefully, studies like these will tell us more. In fact, patients are generally more reluctant than physicians to discontinue their medication when in remission."

What do you think are the implications for everyday practice of your findings?

"We should use immunomodulators together with ADA as well as IFX. This has been debated, because in theory ADA should induce less immunogenicity. I think that our data tell you that you should use immunomodulators the first 6-12 months alongside any TNFi. On the other hand, I do not believe our data will influence the choice of treatment in the first or second line. The perspective could change once IFX will be available as subcutaneous injection. This may have a negative impact on its drug survival concerning adherence since the patient will no longer need to come to the hospital for administration."

References

1. Lirhus SS, et al. ECCO 2019, P191.
2. Lirhus SS, et al. ECCO 2019, P221.
3. Bots SJA et al. Neth J Med. 2017;75(10):432-42.
4. Ryan T, et al. ECCO 2019, P557.

Basic and Preclinical Research

Pathogenesis

Research leading to new insights into the pathogenesis of inflammatory bowel disease (IBD) highlighted the roles of: PTPN2 SNP in the pathogenesis of fibrosis in Crohn's disease (CD); Proteus, Gram-negative facultative anaerobic bacilli in mediating inflammation in CD; and BUB1 (budding uninhibited by benzimidazoles-1) in the development of CD.

In patients with fibrostenotic CD, loss of PTPN2 function associated with rs7234029 in ileal subepithelial myofibroblasts (SEMF) leads to increased phosphorylation of pSTAT3 (Y705), and also results in the excess collagen I production and proliferation that occur in these patients' strictures [1]. These consequences of rs7234029 expression in fibrostenotic CD were found by studying primary SEMF cultures isolated from ileum of patients with Montreal B2 CD that were either naïve, transfected with wtPTPN2, or were used for CRISPR/Cas9-mediated PTPN2 gene deletion. Increased basal Y705, pErk1/2, collagen I production and proliferation in SEMF of strictured ileum were normalised by inhibition of STAT3 phosphorylation or expression of dominant negative STAT3 (Y705F). Despite a 3-fold increase in PTPN2 protein in strictured SEMF in these cells, levels of STAT3 phosphorylation were also increased, suggesting a loss of phosphatase function. This function was restored by wtPTPN2 expression, resulting in lowered levels of Y705.

The role of Proteus, Gram-negative facultative anaerobic bacilli, as a gut pathogen in mediating inflammation in CD was investigated. A urease producing organism in the gut called *P. mirabilis* was found to be associated with CD and can induce inflammation in cell lines and animal models of colitis [2]. Dr Jiangwen Zhang (University of Hong Kong, Hong Kong) et al. suggest that *P. mirabilis* and related species may act as a pathobiont, and, thus, play a critical role in the pathogenesis of CD.

The prevalence of Proteus in faecal samples was higher in CD patients than in healthy controls ($P<0.05$). Proteus levels were significantly increased in CD biopsies compared with control tissue. The 24 Proteus-monoclones isolated from faeces and biopsy of CD patients all belonged to members of *P. mirabilis* lineages. Proteus gavaged mice had a shortened colon compared with mice treated with E. coli 1655 ($P<0.05$). Mice depleted of bacteria and exposed to Proteus and DSS showed significantly higher severity of inflammation. Of cells co-cultured with Proteus, 70-80% were unhealthy or dead. Increased necrotic cells were found in 4 cell lines co-cultured with Proteus due to bacterial invasion. Moreover, Proteus stimulated the production of pro-inflammatory cytokines including IL-18 ($P<0.001$) and IL-1α ($P<0.01$) and induced key pro-inflammatory pathways.

BUB1 (budding uninhibited by benzimidazoles-1) is a serine/threonine-protein kinase that was recently found to mediate TGFβ-dependent signalling. BUB1 was discovered to induce fibrosis in the gut. Thus, it might be a potential target for intestinal fibrosis associated with CD [3]. Dr V. Garlatti (Humanitas University, Italy) explained that BUB1 expression levels were increased within the muscularis mucosa and muscularis propria of inflamed tissues, particularly when fibrosis was evident.

In vivo, intramural injection of AdBUB1 caused significant elevation of tissue BUB1 levels, transmural inflammatory cell infiltration, and transmural fibrosis in mice colorectum. Moreover, BUB1 inhibition remarkably reduced collagen deposition in colitic mice and significantly improved 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced chronic colitis. *In vitro*, BUB1 inhibition reduced collagen deposition and growth rate of CD-isolated myofibroblasts.

1. Li C, et al. ECCO 2019, OP02.
2. Zhang P, et al. ECCO 2019, P834.
3. Garlatti V, et al. ECCO 2019, OP33.

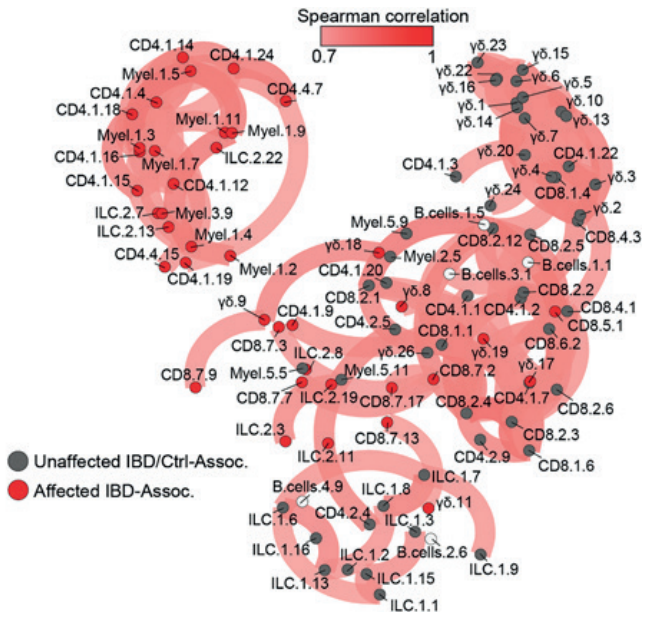
Immune cells and microbes: a happy marriage?

A coordinated cellular network of innate as well as adaptive immune cell types are implicated in inflammatory bowel disease (IBD). This was concluded from a comprehensive analysis of the cell composition in intestinal biopsies from IBD patients across all major immune lineages simultaneously, using high-dimensional mass cytometry [1].

In patients with a clinical suspicion of IBD, paired biopsies from ileum and colon were taken, as well as blood samples in

23 IBD patients and 15 controls with a normal colonoscopy. A total of 309 distinct cell clusters from the collective intestinal dataset were identified containing 3.4 million cells. Affected samples from the different subgroups of IBD (Crohn's disease, ulcerative colitis, and indeterminate colitis) were mostly intermixed, suggesting similarities in the immune profiles. Also noted, was a large interindividual variation in the immune cell composition, which was indicative of unique individual 'immune fingerprints' in the intestinal tract. Comparing affected-IBD samples and unaffected-IBD samples, 19 subsets were significantly different. Several CD4+ T cell clusters correlated with innate lymphoid cells (ILC) and myeloid cell clusters and were up-regulated in IBD-affected segments (see Figure, top-left network). In particular, T cell receptor (TCR) γδ cell clusters (see Figure, top-right network) and a group of ILC clusters (see Figure, bottom network) were up-regulated in unaffected samples of patients and controls.

Figure: Network representation of immune cell cluster correlations [1]



CD, Crohn's disease; IBD, inflammatory bowel disease; ILC, innate lymphoid cells.

Together with the evidence for the unique individual-specific composition of the intestinal immune system, these findings may aid in the development of more (cost-)effective and personalised treatments.

In another study, scientists from Oxford, United Kingdom, assessed host-microbial functions in primary sclerosing cholangitis-inflammatory bowel disease (PSC-IBD) and evaluated whether PSC-IBD-associated pathways affect epithelial transformation [2]. A distinct transcriptomic profile in the caecal biopsies of patients with PSC-IBD compared with ulcerative colitis and haemorrhagic colitis was identified, with 890 genes being regulated in PSC-IBD. This profile in the colonic mucosa of patients with PSC-IBD showed altered regulation of pathways, previously associated with IL-22 and TGFβ signalling. Both these cytokines have been implicated in cancer pathogenesis. PSC-IBD-associated Th1 responses may result in increased epithelial IL-22 responsiveness. Higher expression of the cancer stemness genes OLFM4 and POU5F1 (both associated with pluripotency and early stages of neoplastic transformation) was triggered by bacteria and IL-22 via STAT3 activation. This suggests that microbial-driven IL-22 responses may contribute to epithelial transformation.

Further, emergent date suggest IL-33 and its receptor, ST, might provide a critical contribution to inflammation-driven tumorigenesis, which can lead to colorectal cancer (CRC) [3]. This was the incentive for Dr Loris Lopetuso (Catholic University of the Sacred Heart, Italy) et al. to study the precise contribution of IL-33/ST2 axis in the azoxymethane (AOM)/dextran sodium sulphate (DSS) model of colitis-associated CRC. The results showed that the IL-33/ST2 axis promotes tumorigenesis in colitis-associated CRC through the activation of CD73.

IL-33, ST2L, and sST2 mRNA transcripts were dramatically elevated in AOM/DSS-treated wild-type mice vs knock-out control mice. Localisation of IL-33 to the colonic epithelium and to cells within the lamina propria was morphologically consistent with tissue macrophages in treated wild-type mice. ST2 staining was localised to the intestinal epithelium in tissues immediately adjacent to tumours; within the tumours themselves, ST2+ cells displayed a spindle/fibroblast-like morphology, with a unique distribution throughout the polyps. Little or no staining for both IL-33 and ST2 was present in controls. FACS analysis showed a distinct population of CD45+ haematopoietic cells, consisting of CD3/CD8+ cytotoxic T cells (CTLs), CD19+ B lymphocytes, CD11b+CD11c- and CD11b+CD11c+ myeloid cells. CD45-ST2+ and CD45+ST2+ expressed significantly elevated levels of CD73 compared with ST2-cells. AOM/DSS treatment in IL-33, ST2 knock-out, and CD73 knock-out mice resulted in a significant decreased polyp number and size vs wild-type mice.

1. Van Unen V, et al. ECCO 2019, OP27.
2. Neyaz M, et al. ECCO 2019, OP28.
3. Lopetuso LR, et al. ECCO 2019, OP29.

Moving towards new therapeutic options

Pharmacological inhibition of autophagy was shown to exacerbate intestinal inflammation, fibrosis, and epithelial-mesenchymal transition (EMT) in a murine model [1]. In intestinal resections from Crohn's disease patients, expression of autophagy markers correlated with expression of pro-fibrotic and pro-EMT genes.

Intestinal fibrosis was induced using the heterotopic transplant model. Segments of 1 cm colon from mice were subcutaneously transplanted into the neck of a recipient mice and collected after 7 days. Recipient mice were treated with a daily injection of autophagy inhibitor 3-MA (10 mg/kg). The results showed a significant increase in the expression of proinflammatory genes such as TNF-α, IL-1β, and IL-6. There was an increase in the expression of profibrotic genes such as Col1a1 and Vimentin. The expression of EMT genes such as Snail1 was significantly increased. Autophagy inhibition by 3-MA was confirmed by western blot, showing an increase of p62 and phospho-mTOR and a reduction in LC3. In intestinal resections from Crohn's disease patients, the expression of p62 positively correlated with the expression of Col1a1 (P=0.004), α-sma (P=0.041), Snail1 (P=0.0003), and Snail2 (P=0.0009).

Dutch scientists showed that a high dose of mesenchymal stromal cells (MSCs)-derived exosomes is able to counteract epithelial damage *in vitro* and partially reduce colitis *in vivo* [2]. They isolated exosomes from the conditioned medium (CM) of MSCs and visualised them using electron microscopy. PKH-labelled exosomes showed fusion with epithelial cells *in vitro* after 24 hours. MSC–CM and a high-exosome concentration were found to increase epithelial cell survival/proliferation and cell migration, and also enhanced the proliferation of non-damaged epithelial cells compared with non-CM and a low concentration of exosomes. Furthermore, in vivo experiments showed that endoscopic injections with a high dose of exosomes partially reduced dextran sodium sulphate (DSS)-induced colitis, demonstrated by a higher relative body weight and lower endoscopic disease score than PBS-treated mice. These results encourage further exploring cell-free MSC-related therapy in inflammatory bowel disease (IBD) by using MSC-exosomes.

Scientists from London investigated whether selective regulation of human colonic γδ cells by BTNL3+8 is perturbed in IBD, and examined factors that may modulate this. They described an important axis by which epithelial cells maintain homeostasis of the γδ T cell compartment, which is frequently dysregulated in IBD [3]. Their data supports the use of IL-12 blockade in restoring this axis, while IL-23 may be redundant in this setting, with implications for future therapeutic strategies. They also claimed that therapeutic blockade of αEβ7 has the potential to disrupt an important axis in the human colon which may exacerbate disease given the precociously active, pro-inflammatory nature of αEβ7-γδ T cells.

1. Cosin-Roger J, et al. ECCO 2019, OP03.
2. Barnhoorn M, et al. ECCO 2019, OP22.
3. Dart RJ, et al. CCO 2019, OP32.

Genetics

Novel host-microbiome interactions in inflammatory bowel disease

Scientists from Groningen (the Netherlands) and Boston (USA) performed what they claimed to be the largest, high-resolution, genome–microbiome association study to date using whole-exome sequencing and metagenomics sequencing methods [1]. Disease-specific interactions were explored in the context of inflammatory bowel disease (IBD), including the effect of risk loci and protein-truncating variants.

Whole-exome sequencing of the host genome, and whole-genome shotgun sequencing of faecal samples of 524 IBD patients and 939 controls from a population-based cohort were performed. The interaction between exonic variants, microbial taxa, and metabolic pathways was explored using a four-step approach:

1. A bidirectional meta-analysis between the 2 cohorts to identify common variants.
2. A targeted meta-analysis of IBD risk loci and protein-truncating variants (PTVs).

3. A gene-based burden test to detect rare mutations that affect microbial features.
4. An interaction analysis to identify IBD-specific microbial quantitative trait loci (mbQTLs).

In 170,000 protein-coding variants and 641 microbial features, 26 associations between genetic variants and gut microbial features (FDR<0.05) were identified. Among common variants, a strong mbQTL was observed for deletion near the IBD-risk *IL17REL* gene that was correlated to *Alistipes indistinctus* abundance, known to be decreased in IBD patients. Mutations in an IBD-related gene *CYP2D6*, a major component of phase I drug metabolism, were associated with decreased bacterial biosynthesis of vitamin K (PWY-5838). The *GPR151* gene, which protects against obesity and type II diabetes, was found to be associated with a decrease in bacterial degradation of glucose. The interaction analysis revealed another association between *BTNL2* and bacteroides specific to IBD. These results highlight the importance of host genetics in the maintenance of gut microbiome homeostasis critical for prevention of IBD.

1. Hu S, et al. ECCO 2019, OP01.

Molecular effects of ustekinumab

To provide insight into the molecular effects of ustekinumab in ulcerative colitis (UC) patients, transcriptomic and protein analyses were performed in the first ~60% of patients who were randomised in the UNITI phase 3 induction study of ustekinumab [1]. The results demonstrated the suppression of IL-12 (IFN γ) and IL-23 (IL-17A) pathways and normalisation of the UC disease gene expression profile in response to ustekinumab.

Colonic biopsy mRNA and serum samples were analysed of patients with a history of biological therapy failure (BF) and those without (BN). Samples from healthy subjects were analysed as controls. Biopsies from UC patients had a gene expression disease profile of 4,095 probe sets, including genes involved in inflammatory response, tissue remodelling and wound healing, host-microbe interaction, intestinal permeability, and solute transport. BF and BN patients shared almost identical disease profiles.

At baseline, BF and BN patients had similar serum profiles with significantly elevated levels of IFNγ, IL-17A, IL-22, SAA, NGAL, MMPs, and TNF compared with the healthy controls. Normalisation of IFNγ, SAA, IL-17A, and IL-22 was first detected in responders to ustekinumab at week 4, and continued to improve through week 8. A trend of normalisation of MMPs, IL-10, and NGAL was observed in ustekinumab responders; this trend was weaker or absent in ustekinumab non-responders and placebo-treated patients. TNF was elevated in UC prior to treatment and was not normalised by ustekinumab induction therapy.

1. Li K, et al. ECCO 2019, OP13.

Gene expression signature predicts non-response

The molecular profile score (MPS) consistently predicted non-responders to therapy in 4 independent trials of TNF-antagonists in inflammatory bowel disease (IBD) and an anti-IL-12/23 trial in Crohn's disease [1]. This ability was regardless of ethnicity or whether the therapy targeted TNF or IL-12/23 pathways. Clinical parameters and inflammatory markers by themselves lack the granularity to identify this subset of non-responder patients.

The MPS consisted of a colonic 13-gene expression panel. It accurately predicted non-responders, as defined by lack of mucosal improvement, to TNF-antagonist therapy in UC in all 4 independent clinical trials. There was a high negative predictive value of 0.78 in the ACT1 trial, 0.79 in PURSUIT-SC, 0.89 in PROgECT, and 0.73 in PURSUIT-J. In addition, the MPS could predict non-responders, as defined by lack of endoscopic response, to anti-IL-12/23 therapy in the UNITI trial, with a negative predictive value of 0.85. Non-responders, as predicted by MPS, did not differ from predicted responders in baseline disease severity, nor in baseline inflammatory markers including C-reactive protein, faecal calprotectin, or faecal lactoferrin levels. Transcriptomics and microbiome analysis revealed potential ways to treat these predicted non-responders, as they had 268 differentially expressed genes enriched in inflammatory pathways and demonstrated significant microbial dysbiosis. The MPS is now the first prospectively validated predictive biomarker that can accurately identify a discrete subset of non-responder patients to 2 different anti-inflammatory therapies. It may be valuable in identifying subsets of patients in need of treatment with alternative therapies or for patient stratification in clinical trials.

1. Sato T, et al. ECCO 2019, OP36.

ZNF133 associated with infliximab response

Korean scientists identified clinical and genetic markers associated with infliximab response in patients with inflammatory bowel disease (IBD) [1].

Korean IBD patients (n=139) who were treated with infliximab were classified as either: primary response vs non-response, or sustained response vs loss of response. An association study was conducted using whole-exome sequencing data to identify genetic variants associated with infliximab response. Candidate variants were validated in 77 German patients with IBD.

Five candidate variants were found that were associated with primary non-response to infliximab (P<5×10−6). Of these variants, rs2228273 in *ZNF133* was validated in German patients (combined P=6.49×10−7). The best genetic variant associated with loss of infliximab response was rs9144 (P=4.60×10−6). In multi-variate regression analysis, rs2228273 (P=2.10×10−5), concurrent azathioprine/6-mercaptopurine use, and body weight at the first infliximab use (<50 kg) were associated with primary non-response. In addition, the Crohn's disease activity index (CDAI) at the time of first infliximab use, as well as rs9144 (P=0.001), were independently associated with loss of response in Crohn's disease patients. These findings could provide insights to maximise the efficacy of infliximab therapy in IBD.

1. Jung ES, et al. ECCO 2019, DOP55.

Network analysis of GWAS

Greek researchers reported on their use of a novel approach that ranks proteins and signalling pathways associated with inflammatory bowel disease (IBD) phenotypes by disease implication [1].

This provided new insights into IBD's molecular background, and highlights targets of potential diagnostic and therapeutic value. They performed a network analysis of GWAS of an extended cohort of 573 Greek IBD patients (364 with Crohn's disease and 209 with ulcerative colitis) and 445 controls. They implicated 89 loci in IBD risk. Also, distinct functional pathways associated with each of the 2 IBD forms and their phenotypes were identified. For most of the IBD susceptibility loci, the direction and magnitude of effect were consistent in IBD cohorts. Phenotype-specific functional interaction networks, through centrality analysis, revealed well known IBD-related genes and their interactors.

1. Gazouli M, et al. ECCO 2019, P828.