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12th Congress of the European Crohn's and Colitis Organisation

New highlights on treatment of UC using vedolizumab

Studies on Mayo Clinic Scores, Endoscopic Subscore and Stool Frequency Score showed improvement of Quality of Life in UC patients with a severe disease course.

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Pathophysiology, diagnosis and complications

Presenters explored the genetic architecture of IBD across the entire allele frequency spectrum. UC associated dysplasia and neoplasia can be accurately predicted by a five marker methylation marker panel.

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Crohn's Disease

Research using abrilumab demonstrated beneficial effects for remission and response rates in CD patients.

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Editor Prof. dr. C. Janneke van der Woude, Erasmus MC Rotterdam, The Netherlands

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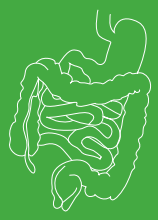

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Letter from the Editor

Prof. Dr. C. Janneke van der Woude, MD, PhD

Dear Reader,

The incidence of inflammatory bowel disease (IBS) continues to rise. This means that it is more important than ever for researchers, medical professionals from a broad range of fields related to IBD, including gastroenterology, internal medicine, surgery, paediatrics, epidemiology, endoscopy, imaging, nursing, pathology, dietitians and other experts to come together and discuss the future of both Ulcerative Colitis (UC) and Crohn's Disease (CD). This is why the annual congress of the European Crohn's Disease and Colitis Organisation (ECCO) is very important. For 2017 this year's theme is 'Advancing knowledge, improving care'.

Here, we present the highlights from the recent ECCO congress that was held in sunny Barcelona, the largest forum for IBD specialists in the world. Clinically relevant topics and key outcomes have been selected. I hope that you enjoy our selection.

With kind remarks,

Prof. Dr. Janneke van der Woude

Biography

As a professor in the department of Gastro-enterology and Hepatology of the Erasmus MC, Rotterdam, The Netherlands, Janneke van der Woude is involved in optimising care for patients with inflam-matory bowel diseases (IBD). Her PhD thesis (2004) is entitled "Apoptosis in (pre-) malignant lesions in the gastrointestinal tract". She leads the clinical IBD unit and research on the different aspects of IBD, and it has been done in cooperation with the departments of Pediatric Gastroenterology, Surgery, Pathology, Psychology and Internal Medicine. The research line focuses on new methods for treatment of IBD, improved quality of life for IBD patients and gender diversity in IBD.

Treatment options in IBD

JAK-inhibitors

Filgotinib

Filgotinib – an oral, selective Janus kinase 1 (JAK1) inhibitor – has shown good efficacy and a tolerable safety profile in patients with moderate-to-severely active Crohn's disease (CD) in a Week 10-20 period of a 20-week phase 2 study. A total of 174 patients with moderate-to-severely active CD and confirmed ulcerations were randomised 3:1 to receive 200 mg filgotinib or placebo once daily (QD) for 10 weeks. Immunosuppressives were to be discontinued prior to treatment initiation but corticosteroid-treated patients remained on stable doses until week 10. Based on clinical response at week 10, patients were assigned to filgotinib 200 mg or 100 mg QD or placebo for an additional 10 weeks. Patients assessed as clinical responders underwent mandatory corticosteroid tapering after week 10. It was shown that 50-71% of initial filgotinib 200 mg responders showed clinical remission; 67-79% showed a clinical response, depending on their assignment to filgotinib 200 mg QD, filgotinib 100 mg QD or placebo. The filgotinib initial responders also maintained their gains in quality of life (QoL; the Inflammatory Bowel Disease Questionnaire (IBDQ) score at week 20 was at least 38.1 points higher than baseline). 59% of patients not responding to placebo after 10 weeks showed clinical response at week 20 upon being switched to filgotinib 100 mg QD with 32% showing clinical remission. Treatment-emergent adverse events (TEAEs) occurred in 75% of patients on filgotinib (covering all periods of filgotinib exposure) and in 67% of placebo patients (covering all periods of placebo exposure). Serious TEAEs occurred in 9% of patients being treated with filgotinib and in 4% of placebo patients. This led to discontinuation of treatment in 18% of filgotinib patients and in 9% of placebo patients. Serious infections were reported in 3% of filgotinib patients: there were none in the placebo group. The researchers concluded that clinical efficacy, induced with filgotinib after 10 weeks of treatment, as well as IBDQ improvements were sustained through week 20 despite mandatory steroid tapering. Although 100 mg filgotinib also showed efficacy, further evaluation is needed. Furthermore, the efficacy and safety data of filgotinib suggest a favorable risk/benefit profile [1].

Tofacitinib

Tofacitinib – an oral, small molecule JAK-inhibitor - has been assessed in a number of studies involving CD as well as ulcerative colitis (UC). In 150 patients with moderate to severe CD, data from an open-label long-term extension study evaluated efficacy and safety of tofacitinib 5 mg (N=62) and 10 mg (N=88) twice daily (BID). At week 48, 87.9% and 55.6% of 5 and 10 mg BID patients were in remission, with a mean Crohn's Disease Activity Index (CDAI) change from baseline of -4.8 and -121.9, respectively. It emerged that both doses had similar adverse event (AE) rates of which gastrointestinal (GI) disorders and infections were the most common AE system organ classes (SOC). Serious AEs (SAEs) and early discontinuation of treatment due to AE rates were higher in the 10 mg BID group (SAEs: 8.1% for the 5 mg group vs 19.3% in the 10 mg group and discontinuation due to AEs was 11.4% vs 4.8%, respectively for the 10 mg and 5 mg group). However, only patients who were treated with 10 mg BID entered the study with active disease and some patients switched dose groups post-week 8. This study showed no new safety findings regarding tofacitinib from those previously reported [2].

Tofacitinib was also assessed in patients with UC. The OCTAVE Sustain study evaluated tofacitinib in patients who had completed the OCTAVE Induction 1 or 2 study with an at least clinical response. Patients were re-randomised to maintenance treatment with placebo (N=198), tofacitinib 5 mg BID (N=198) or 10 mg BID (N=197) for 52 weeks. The findings showed that tofacitinib 5 and 10 mg BID were significantly more effective compared to placebo as maintenance therapy over 52 weeks in patients with moderately to severely active UC. Despite a dose-dependent increase in herpes zoster (HZ), overall, the observed AE rates were similar among both tofacitinib groups. No new safety findings emerged from those previously reported in studies of rheumatoid arthritis (RA; Table 1) [3].

Anti-TNF treatment

Infliximab biosimilar CT-P13

An Italian prolonged follow-up of a prospective, nationwide, multicentre, observational cohort evaluated safety and clinical/endoscopic efficacy of infliximab biosimilar CT-P13 in 680 patients (CD N=373; UC N=307). A total of 400 patients consisted of patients who were anti-tumor necrosis factor alpha (TNFα)-naïve (CD N=192; UC N=208), 171 patients (CD N=115; UC N=56) had a previous exposure to one or more biologics, whereas the remaining 109 patients (CD N=66; UC N=43) were switched after a mean of 18 previous infusions of infliximab. A total number of over 4,000 infusions was recorded. Primary failure was seen in 8.1% of patients; 45.6% of patients were in remission and 30.9% were considered responders;

Table 1 Summary of efficacy and safety through 52 weeks in OCTAVE Sustain [3]

	Placebo N=198	Tofacitinib 5 mg BID N=198	Difference from placebo (95% CI)	Tofacitinib 10 mg BID N=197	Difference from placebo (95% CI)
Remission at Week 52, n(%)[1]	22 (11.1)	68 (34.3)***	23.2 (15.3, 31.2)	80 (40.6)***	29.5 (21.4, 37.6)
Sustained remission, n(%)[2]	10 (5.1)	44 (22.2)***	17.2 (10.6, 23.7)	50 (25.4)***	20.3 (13.5, 27.1)
Mucosal healing at Week 52, n(%)	26 (13.1)	74 (37.4)***	24.2 (16.0, 32.5)	90 (45.7)***	32.6 (24.2, 41.0)
Sustained mucosal healing, n(%)[2]	13 (6.6)	55 (27.8)***	21.2 (14.1, 28.3)	65 (33.0)***	26.4 (19.0, 33.8)
Sustained steroid-free[3] remission among remitters at baseline, n/N (%)	3/59 (5.1)	23/65 (35.4)***	30.3 (17.4, 43.2)	26/55 (47.3)***	42.2(27.9, 56.5)
Clinical response at Week 52, n(%)	40 (20.2)	102 (51.5)***	31.3 (22.4, 40.2)	122 (61.9)***	41.7 (32.9, 50.5)
Sustained clinical response, n(%)[2]	38 (19.2)	97 (49.0)***	29.8 (20.9, 38.7)	117 (59.4)***	40.2 (31.4, 49.0)
Treatment-emergent AEs, n(%)	149 (75.3)	143 (72.2)	-	156 (79.6)	-
Treatment-emergent SAEs, n(%)	13 (6.6)	10 (5.1)	-	11 (5.6)	-
Infections, n(%)	48 (24.2)	71 (35.9)	-	78 (39.8)	-
Herpes zoster, n(%)	1 (0.5)	3 (1.5)	-	10 (5.1)	-
Serious infections, n(%)	2 (1.0)	2 (1.0)	-	1 (0.5)	-
Malignancies (excluding NMSC)	1 (0.5)	0 (0.0)	-	0 (0.0)	-
NMSC	1 (0.5)	0 (0.0)	-	3 (1.5)	-
Discontinuations due to AEs, n(%)	37 (18.7)	18 (19.1)	-	19 (9.7)	-

***P<0.001 vs placebo; [1] primary endpoint; [2] sustained endpoints were defined as achieving response/remission at both Week 24 and Week 52; [3] steroid-free was defined as not requiring corticosteroids for ≥4 weeks prior to each visit.
Patients entering OCTAVE Sustain could be receiving a maximum of prednisone 25 mg/day or equivalent. Steroid tapering was mandatory at baseline, with all patients steroid-free by Week 7.
Binary efficacy data are full analysis set, non-responder imputation and compared using Cochran-Mantel Haenszel chi-square test AE, adverse event; BID, twice daily; CI, confidence interval; LS, least squares; NMSC, non melanoma skin cancer; SAE, serious AE.

10.3% lost the response. The remaining patients were a failure or stopped the therapy. After 1 year of CT-P13 therapy, Harvey-Bradshaw Index (HBI), Simple Endoscopic Score for Crohn's Disease (SES-CD), C-reactive protein (CRP), and calprotectin significantly (P<0.01) were reduced in CD patients compared to baseline as was the case for Partial Mayo (PM), endoscopic Mayo (EM), CRP and calprotectin in UC patients (P<0.001). A deep remission was achieved in 57% and 50% of CD and UC patients of whom all information was available. A total of 13.5% SAEs was reported, which lead to discontinuation of the biosimilar in 10.7% of patients. This was also the case in 5.6% of patients for injection reaction (IRs); these were significantly more frequent in patients who had been pre-exposed to anti-tumour necrosis factor (TNFα) (P<0.02) [4].

Infliximab

Long-term follow-up of the TAXIT trial (with a median follow-up of 41 months) demonstrated that infliximab discontinuation occurred earlier in patients treated in the clinically-based dosing arm than in patients treated in the concentration-based dosing arm. It emerged that 78% of patients were still on continued treatment with infliximab, whilst 22% of patients needed to stop (11 patients were lost to follow-up). Of those patients who stopped treatment, 37% randomised previously to the clinically-based dosing arm did so within 1 year, compared to 10% of patients randomised to the concentration-based dosing arm (P<0.05). Among those patients who continued infliximab, the dosing scheme was intensified in 56 patients and de-intensified in 27 patients, compared to the end of the TAXIT maintenance phase. Median trough concentrations of infliximab at the end of follow-up were 4.73 µg/mL. In patients who continued infliximab, the rate of inflammatory bowel disease (IBD)-related hospitalisation was 9.6%; for abdominal surgery, this was 2.4% and for steroid use 3.6% during the entire follow-up period (Table 2).

Table 2 Outcome parameters in patients who continued infliximab vs patients who discontinued infliximab [5]

	Continuation of infliximab (N=167)	Discontinuation of infliximab (N=48)	P-value
Hospitalisation	16 (9.6%)	16 (33.3%)	< 0.001
Abdominal surgery	4 (2.4%)	10 (20.8%)	< 0.001
Steroid use	6 (3.6%)	16 (33.3%)	< 0.001

Adalimumab

The duration and effectiveness of adalimumab treatment in pediatric CD patients in clinical practice without prior anti-TNF therapy was assessed in an American retrospective cohort study. This included a total of 174 patients (57% male and 25% was < 13 years old at induction) who were treated with adalimumab from August 2008 to December 2015. The numbers and percentages of patients achieving steroid-free remission and steroid-free response on either Physician Global Assessment (PGA) or Short Pediatric Crohn's Disease Activity Index (sPCDAI) on different time points are outlined in Table 3 [12].

Table 3 Durability and clinical effectiveness of adalimumab in anti-TNF naïve pediatric CD patients [12]

Features	Baseline	3 months	6 months	12 months	24 months	36 months
Patients being followed for this duration post-induction	174	174	174	154	71	39
Patients remaining on adalimumab [n, (%)]	174 (100%)	174 (100%)	166 (95%)	145 (94%)	69 (97%)	31 (80%)
Steroid free remission-PGA						
Yes	25 (15%)	110 (69%)	120 (75%)	112 (79%)	64 (94%)	25 (81%)
No	145 (85%)	49 (31%)	40 (25%)	30 (21%)	4 (6%)	6 (19%)
Steroid free remission-sPCDAI						
Yes	39 (32%)	97 (71%)	106 (77%)	91 (80%)	42 (91%)	19 (86%)
No	85 (68%)	39 (29%)	32 (23%)	23 (20%)	4 (9%)	3 (14%)
Steroid free response-PGA						
Yes	82 (48%)	140 (88%)	146 (91%)	132 (93%)	67 (99%)	29 (94%)
No	88 (52%)	19 (12%)	14(9%)	10 (7%)	1 (1%)	2 (6%)
Steroid free response-sPCDAI						
Yes	55 (44%)	113 (83%)	117 (85%)	104 (91%)	45 (98%)	22 (100%)
No	69 (56%)	23 (17%)	21(15%)	10 (9%)	1 (2%)	0 (0%)

It needs to be noted that concomitant immunomodulatory therapy did not appear to improve the outcomes. These findings from the largest series with the longest follow-up showed that adalimumab was durable and effective as initial anti-TNF therapy for pediatric CD in clinical practice. Of the patients who were followed for 24 months, 97% remained on adalimumab. Steroid-free clinical remission was achieved in 91%-94% and steroid-free clinical response in 98%-99%, of patients who remained on adalimumab for 24 months. The effect of dosage on outcomes is currently being investigated [12].

Anti-IL12/23

Ustekinumab

Ustekinumab – a fully human IGG1 monoclonal antibody to human IL 12/23p40 – was evaluated in the IM-UNITI long-term extension study for efficacy and safety of subcutaneous ustekinumab trough approximately 5 years of treatment. The week 96 results, involving 1,281 patients, showed that subcutaneous ustekinumab maintained clinical response and remission trough two years, with no new safety signals being observed [13].

Anti-integrin

Etrolizumab

The HICKORY study evaluated the safety and efficacy of etrolizumab – an anti-β7 monoclonal antibody targeting integrins α4β7 and αEβ7 – during induction and maintenance in 130 αTNF-refractory or intolerant (IR) patients with moderate-to-severe UC. A total of 97% patients received all induction doses. The rectal bleeding remission rates improved from baseline to week 4 (approx. 30%) and 14 (approx. 50%). Stool frequency remission rates improved from baseline to week 4 (approx. 10%) and 14 (approx. 25%). Patient-reported outcome (PRO) scores (stool frequency + rectal bleeding) improved regardless of disease severity and irrespective of prior treatment with 1 or ≥ 2 anti-TNFs. The mean decrease in PRO was 22% at week 4 and 36% at week 14; this decrease mirrored mean reductions in faecal calprotectin and CRP. Overall, the faecal calprotectin and CRP levels decreased at week 14 by a mean of 57% and 33%, respectively. Mean decrease in CRP in patients with CRP levels > 2.87 mg/L (upper limit of normal (ULN) at baseline was 47%). Mean decreases in faecal calprotectin and CRP levels at week 14 were greater in patients in stool frequency remission (faecal calprotectin, 83%; CRP, 54%) and in patients in rectal bleeding remission (faecal calprotectin, 69%; CRP, 49%). The safety and tolerability profile as seen with etrolizumab was favorable [7].

Vedolizumab

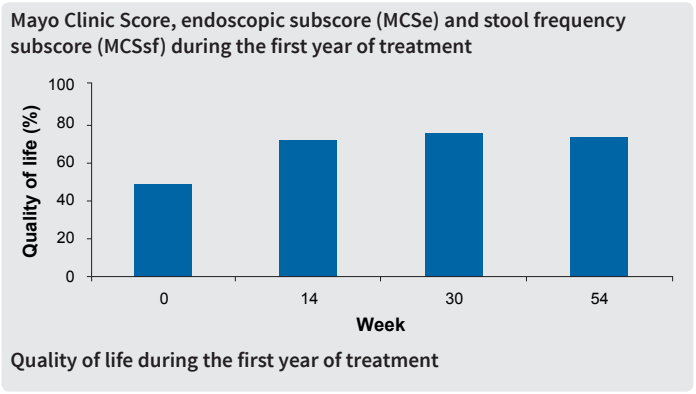
A post hoc analysis of the GEMINI 1 study assessed sustained remission during the maintenance phase of GEMINI 1 in UC patients who were treated with vedolizumab. Patients enrolled in GEMINI 1 received 6 weeks of induction with placebo or vedolizumab and entered 46 weeks of maintenance continuing placebo or vedolizumab, respectively. Eligible patients could then enroll into an open-label extension to receive vedolizumab every 4 weeks. The primary aim was to assess sustained remission (remission at weeks 26, 38 and 52) in patients who achieved remission at week 14. In total, 620 patients were treated with vedolizumab (week 6 responders and non-responders) and 149 received placebo throughout GEMINI 1. From week 4 onwards, a significantly higher proportion of patients receiving vedolizumab were in clinical remission vs placebo in the overall and anti-TNF-naïve populations; significance was achieved at week 26 in the anti-TNF failure population. At week 14, 33% of patients receiving vedolizumab and 20% of patients receiving placebo were in clinical remission based on Partial Mayo Score (PMS). 47% of patients who received vedolizumab and 29% of patients receiving placebo were in remission based on rectal bleeding subscore. Of those patients in remission at week 14, the vedolizumab group had a higher proportion of patients

with sustained remission versus placebo according to both PMS and rectal bleeding definitions. Significance was reached in both the overall and anti-TNF-naïve populations and a similar nominal trend was observed in the anti-TNF failure population. Based on these findings, it was concluded that week 6 is most likely too early to ascertain the full clinical benefit of vedolizumab; it showed a significant difference vs placebo in the proportion of patients achieving clinical remission as early as week 4 for the overall and anti-TNF naïve populations. However, the researchers pointed out that as per label, assessment of the clinical benefit should be made after 10-14 weeks. In patients with remission at week 14 in GEMINI 1, continued vedolizumab treatment resulted in approx. 60% of patients maintaining sustained remission based on PMS and rectal bleeding sub-score [8].

In CD patients who have recently been exposed to anti-TNF agents, lower vedolizumab trough concentrations can be predicted as was shown by a study by van Gils et al. From a total of 75 patients (CD N=46; UC N=29) who started treatment with vedolizumab, the vedolizumab and anti-TNF serum concentrations were measured at trough during the treatment with vedolizumab week 2, week 6, week 10 (CD patients only), week 14 and week 22. It was shown that 46% of CD patients and 66% of UC patients achieved clinical response. However, only in UC patients, an exposure-response relation was found between vedolizumab trough concentration up to week 22 and clinical response (P<0.0001). At week 22, 48% and 32% of the CD patients were in biological response and remission. Patients in biological remission had higher vedolizumab trough concentrations at week 6, week 10 and week 22 (P=0.02, P=0.04 and P=0.01, respectively). Mucosal healing was achieved in 18% of CD patients and in 66% of UC patients. This last category of patients had higher vedolizumab trough concentrations up to week 22 compared to patients who had no mucosal healing (P=0.02, P=0.006, P=0.03 and P=0.04 for week 2, week 6, week 14 and week 22). Patients with CD who achieved mucosal healing had higher vedolizumab trough concentrations at week 6 and week 10 (P=0.006, P=0.03, respectively). 93.3% of patients had previously been exposed to anti-TNF and one third still had detectable anti-TNF concentrations at the first vedolizumab infusion. CD patients who were recently exposed to anti-TNF (< 16 weeks before the start of vedolizumab therapy, N=38) had lower vedolizumab trough concentrations at all time points, compared to patients with no recent anti-TNF exposure. According to the investigators, the inverse association between recent anti-TNF exposure and vedolizumab trough concentrations in CD patients is intriguing and might be explained by a residual effect of anti-TNF treatment on MAdCAM-1 expression [9]. The long-term safety of vedolizumab is being investigated in the GEMINI open-label extension trial. Recently, the 5-year exploratory analyses of effectiveness and safety in patients with CD who had completed GEMINI 2 and were enrolled in GEMINI open-label extension have become available. These showed that long-term vedolizumab therapy (approx. 5 years) was associated with clinical benefits including clinical response, clinical remission and health-related QoL (HRQoL) improvements in patients with moderately to severely active CD who responded at week 6, completed GEMINI 2 and enrolled in open-label extension. Long-term vedolizumab therapy was associated with no unanticipated AEs, and the safety profile was consistent with that previously observed in a 3-year interim analysis of the open-label extension study [10].

A German study investigated the efficacy of vedolizumab in achieving PROs outcomes, especially with regard to bleeding in UC patients with a severe disease course. It transpired that vedolizumab treatment resulted in a rapid and persistent absence of rectal bleeding in one third of patients. Normalisation of stool frequency occurred less frequently and may reflect chronic alterations/damages of the bowel that may not be reverted by anti-inflammatory treatment strategies in this severely ill patient population. The absence of rectal bleeding was associated with a substantial improvement in the QoL of these patients (Figure 1) [11].

Figure 1 QoL outcomes with vedolizumab [11]. However, a substantial percentage of patients still required steroid-treatment to achieve these endpoints [11]



Biological naïve patients

So far, real-world outcomes in patients who are being treated with vedolizumab as a first or second-line biologic are limited. A German descriptive study evaluated vedolizumab treatment patterns/effectiveness in comparison to anti-TNFα agents. Data from 313 patients (vedolizumab 47.0%; anti-TNFα 53.0%) was used with a total of 49.0% of vedolizumab patients and 62.0% of anti-TNFα patients being CD patients. Furthermore, 22.4% of vedolizumab patients and 65.7% of anti-TNFα patients were

biologic naïve. The mean follow-up was 1.4 years and mean age was 41 for vedolizumab patients and 38.5 for the anti-TNFα patients. In biologic naïve patients, median treatment duration was 1.5 years for vedolizumab and 1.2 years for anti-TNFα. A total of 18.2% vedolizumab patients and 18.3% anti-TNFα patients discontinued treatment mostly due to lack of response/inadequate symptom control; 9.1% of vedolizumab patients and 10.1% of anti-TNFα patients switched to a new biologic. 80.4% of vedolizumab patients and 66.7% of anti-TNFα patients with assessable data had documentation of 12-month treatment response (Table 4) [21].

Table 4 Treatment response at 12 months (≥ 9 to < 15 months) for patients with assessable measurements of clinical effectiveness [21]

	VDZ Biologic naïve	VDZ Prior Biologics	Anti-TNF Biologic naïve	Anti-TNF Prior Biologics
N(%)	(N=33)	(N=114)	(N=109)	(N=57)
Patients with assessable data	14 (100)	51 (100)	48 (100)	21 (100)
Positive (improvement)	12 (85.8)	41 (80.4)	39 (81.3)	14 (66.7)
No change	1 (7.1)	7 (13.7)	4 (8.3)	3 (14.3)
Negative (worsening)	0 (0)	0 (0)	0 (0)	1 (4.7)
Unknown	1 (7.1)	3 (5.9)	5 (10.4)	3 (14)

VDZ = vedolizumab

Thus, it was demonstrated that patients who are naïve to biologics, appears to continue vedolizumab treatment longer – but with similar rates of discontinuation, switching of treatment and treatment response – compared to anti-TNFα patients within 1 year. More vedolizumab patients with one prior biologic experienced discontinuations and switching of treatment compared to biologic naïve patients. In prior biologic exposed patients, vedolizumab resulted in a much higher proportion of treatment response compared to anti-TNFα agents [21].

A Finnish real-world study in adult patients showed that vedolizumab is effective and well-tolerated by patients, even among those with treatment refractory IBD. This was assessed in 232 patients (CD N=105; UC N=127) of which 96.1% of CD patients had either moderately or severely active disease; 92.5% of UC patients had either mildly or moderately active disease at baseline. The majority of patients were treatment refractory to the previous anti-TNFα treatment (97.1% of CD patients and 94.5% of UC patients were anti-TNFα experienced). Also, the majority (CD 43.8%; UC, 62.2%) were using concomitant steroids at baseline. Six months post treatment initiation, 73.3% of CD patients and 66.1% of UC patients were persistent on vedolizumab therapy. The most common reason for discontinuation was primary lack of response (CD 63.0%; UC 75.0%), followed by secondary loss of response (CD 7.4%; UC 5.0%), AEs (CD 14.8%; UC 17.5%) and other reasons (CD 18.5%; UC 12.5%) [20].

Abrilumab

Abrilumab - a fully human monoclonal antibody against α4β7 integrin - was studied in 354 patients with UC and inadequate or loss of response to anti-TNFs or immunomodulators. It emerged that abrilumab demonstrated a favorable safety, immunogenicity, pharmakinetic pharmacodynamic and efficacy profile. AEs were balanced among groups trough week 24, with no progressive multifocal leukoencephalopathy (PML) or deaths. No patient developed neutralising antibodies to abrilumab. These findings prompt further testing in subjects with UC. The efficacy did not appear to correlate with peripheral target coverage or changes in α4β7-high Tcm. E-R modeling suggests that higher abrilumab exposure may result in higher remission and response rates [14].

Abrilumab was also assessed in 249 moderate-to-severe CD patients with evidence of the active inflammation as well as inadequate or loss of response or intolerance to immunosuppressant's, TNF antagonists or corticosteroids. Although the primary endpoint of CDAI remission (score < 150) at week 8 was not met, researchers observed beneficial effects of abrilumab for remission and response rates. There was no safety imbalance compared with placebo. However, higher rates of remission and response were observed in the active treatment arms at week 12, particularly in patients with prior failure of TNF antagonists assigned to the 210 mg abrilumab group (Table 5) [15].

Mongersen

Mongersen - an antisense oligodeoxynucleotide complementary to the sequence of Smad7 mRNA - is being evaluated for the treatment of patients with active CD. It is formulated as a gastro-resistant, delayed-release, pH-dependent tablet that delivers active substance to the distal GI tract with negligible systemic exposure. The correlation between clinical and endoscopic indices in a phase 1b study was explored in 63 patients with active CD (CDAI 220–450, total SES-CD ≥ 7, or ileal disease SES-CD ≥ 4). Patients characteristics showed that their mean age was 41.5 years, mean SES-CD was 11.2, mean CDAI was 294 and their mean CD duration was 11.6 years. Furthermore, 46% had prior TNFα exposure and 33% had prior CD surgery. Patients were randomised to 4, 8, or 12 weeks of oral mongersen 160 mg daily, followed by an observation period without study drug. Patients showed improvements in clinical outcomes as early as week 2 in the 4-, 8- and 12-week treatment groups.

Table 5 Patient remission and response rates with abrilumab [15]

Total Patient Population				
		Abrilumab		
	Placebo (N=98)	21 mg Q4W (N=26)	70 mg Q4W (N=84)	210 mg (single dose) (N=41)
CDAI Remission, %				
Week 8	12.8	23.1	14.4	21.9
Week 12	17.6	41.7*	27.9	30.8
CDAI Response, %				
Week 8	27.0	32.4	43.2*	29.4
Week 12	29.6	47.4	48.9*	46.6*
CRP change from baseline at week 8, mg/L, mean (SE)	2.93 (2.16)	1.05 (2.41)	-0.45 (2.03)	-1.43 (2.07)
FCP change from baseline at week 8, mg/L, mean (SE)	-104.26 (186.15)	-534.31 (308.98)	-34.14 (135.15)	141.28 (243.14)
Prior Anti-TNF-Failure Patients				
		Abrilumab		
	Placebo (N=79)	21 mg Q4W (N=20)	70 mg Q4W (N=65)	210 mg (single dose) (N=32)
CDAI Remission, %				
Week 8	5.8	7.6	9.6	16.3*
Week 12	8.2	22.9*	17.4*	24.8*
CDAI Response, %				
Week 8	15.1	16.2	39.3*	27.0
Week 12	14.2	30.0	39.4*	37.4*
Prior Anti-TNF-naïve Patients				
		Abrilumab		
	Placebo (N=19)	21 mg Q4W (N=6)	70 mg Q4W (N=18)	210 mg (single dose) (N=9)
CDAI Remission, %				
Week 8	35.3	70.2	19.1	26.5
Week 12	45.8	76.3	40.4	29.2
CDAI Response, %				
Week 8	63.2	75.0	31.0*	27.4
Week 12	67.4	73.8	42.7	50.7

Data are shown as adjusted rates (%) unless noted. * *P*<0.1 vs placebo; all P-values are nominal. N=number of patients in the analysis set. CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein: FCP=faecal calprotectin.

The clinical response (CDAI decrease ≥ 100) was 21%, 26%, and 29%, respectively. Clinical remission (CDAI < 150) was 16% in the 4-week treatment group, 17% in the 8-week treatment group and 19% in the 12-week treatment group. Mean change from baseline in CDAI was −77.9, −77.2, and −78.6, respectively. These improvements were maintained across all 3 treatment groups over 12 weeks of treatment. The highest rates were observed in the 12-week treatment group with clinical response of 53%, 44%, and 67%, respectively. For clinical remission, this was 32%, 35%, and 48% and for mean change from baseline CDAI this was −124, −113, and −133. A total of 52 patients had evaluable endoscopies at week 12; 37% of these had an endoscopic response (≥ 25% reduction in SES-CD from baseline to week 12), with no meaningful difference across the treatment groups. Among the patients with SES-CD >12, 63% had a ≥ 25% and 31% had a ≥ 50% reduction in CDAI. Change in SES-CD (adjusted for baseline CDAI, SES-CD, and treatment group) showed a moderate correlation with change in CDAI (r=0.37; P=0.01). SES-CD was developed in patients with intact GI anatomy. Examining this relationship in the 32 patients without prior CD surgery showed an improved correlation (r=0.48; P=0.01). The rates for AEs and SAEs were low and similar between treatment groups. Overall, mongersen was generally safe and well tolerated by patients [24].

It has been reported that histological remission serves as a positive prognostic indicator of clinical activity in UC. In the TOUCHSTONE open-label extension, the impact of histologic remission on UC activity during a long-term evaluation of efficacy and safety of ozanimod 1 mg was evaluated. This was a randomised, double-blind, placebo-controlled phase 2 trial designed to assess the efficacy and safety of ozanimod 0.5 mg and 1 mg vs placebo during induction and maintenance in patients with moderate to severe UC. It was established that ozanimod induced and maintained clinical response, clinical remission, endoscopic mucosal healing and histological remission trough weeks 8 and 32. A total of 197 patients were randomised (1:1:1) and treated with daily ozanimod at 0.5 mg, 1 mg, or placebo. Of the initial 197 patients randomised, 86% entered the open-label extension study and received daily ozanimod 1 mg. 77% and 62% completed assessments at weeks 44 and 80. In this analysis, HR was defined as a Geboes score < 2 and clinical remission was defined as rectal bleeding score = 0 and stool frequency score ≤ 1. Of the patients who entered the open-label extension, 27% showed histological remission at the time of open-label extension entry and 34% were in clinical remission. Clinical remission increased to 62% at open-label extension week 32, with 62%, and 55% in clinical remission at open-label extension weeks 44 and 80. At open-label extension weeks 44 and 80, clinical remission was seen in 83% and 80% of those in histological remission at open-label extension entry compared to 55% and 46% of those not in histological remission at open-label extension entry. The proportion of patients in clinical remission increased throughout open-label extension while receiving 1 mg of ozanimod, regardless of prior treatment in the TOUCHSTONE study or histological remission status at open-label extension entry. The highest rates of clinical remission were seen in patients in histological remission at open-label extension entry who had received ozanimod for 32 weeks prior to open-label extension entry, with clinical remission rates at open-label extension weeks 4 and 8, with over 90% in the open-label extension. The lowest clinical remission rates were seen in patients naïve to ozanimod and not in histological remission at open-label extension entry, with clinical remission increasing from 13% at entry to 50% at open-label extension week 8, reaching a peak of 56% at open-label extension week 32.

Overall, treatment with ozanimod for 32 to 36 weeks resulted in clinical remission in 80% of patients. The most common AEs which were observed in the open-label extension were UC flare, back pain, upper respiratory tract infections, anemia, and nasopharyngitis. Transient asymptomatic elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3× ULN were seen in 3% of patients. The researchers concluded that histological remission is predictive of clinical remission in patients with UC receiving ozanimod 1 mg in open-label extension. All patients, whether naïve to or having received ozanimod in TOUCHSTONE, showed additional improvements in clinical remission upon continued treatment with ozanimod 1 mg in open-label extension. Patients naïve to ozanimod had a rapid improvement in clinical remission over the first 8 weeks of treatment with ozanimod 1 mg in the open-label extension [29].

Rectal tacrolimus in proctitis

A randomised, double-blind, placebo-controlled induction trial of rectal tacrolimus in patients with active UC investigated the effects of this treatment. Eleven patients received rectal tacrolimus (0.5 mg/mL), and 10 patients received placebo during 8 weeks. An interim analysis after 20 patients had completed the study demonstrated highly significant differences between the groups. The study was closed due to ethical considerations with patients already recruited allowed to complete the study. The primary endpoint was met in 73% of patients receiving rectal tacrolimus and 10% of patients receiving placebo (P=0.004). Of the secondary endpoints, 45% of rectal tacrolimus patients achieved clinical remission compared to none receiving placebo (P=0.015). Mucosal healing at week 8 was achieved in 73% of patients receiving rectal tacrolimus compared to 10% of patients who received placebo (P=0.004). The IBDQ increased ≥ 16 points over baseline in 45% of the tacrolimus and 20% of the placebo patients (P=0.36). The average PMS was numerically lower in the tacrolimus-treated group compared to placebo at week 2 (4.3 vs 5.8; P=0.15) and week 4 (3.7 vs 5.8; P=0.08) but was significantly lower at week 8 (3.3 vs 6.7; P=0.01). No safety issues were identified with rectal tacrolimus use. These findings showed that rectal tacrolimus was more effective than placebo for induction of a clinical response, clinical remission and mucosal healing in resistant ulcerative proctitis [16].

Perianal fistulising disease

Mesenchymal cell therapy

The ADICROHN pilot study is the first trial to evaluate the co-local administration of autologous adipose-derived stromal vascular fraction (ADSVF) in association with micro fat graft in UC patients with refractory perianal fistulas. This is a prospective, open, non-comparative, single center, phase I-II clinical trial, which includes adult patients who have been diagnosed with complex perianal fistula associated with CD at least for 6 months with controlled luminal disease (CDAI<220). Fistula(s) had to be refractory to conventional treatment. Since October 2015, 9 patients have been treated by this new local treatment (among 10 cc of micro fat and about 30 millions of ADSVF viable cells subsequently injected into the soft tissue around the fistulas). Preliminary efficacy data at week 12 for the first 7 treated patients showed a 71% response and complete healing in 28% of cases, as well as significant reduction of discharge (P<0.001), a significant reduction of severity of perianal disease (P=0.045) and significant improvement of QoL (P=0.039). No SAEs have been observed; the only side effect was a moderate pain on lipoaspiration site [17].

Stem cell therapy with Cx601

Complex perianal fistulas could be treated successfully with stem cell therapy, as data from the randomised phase 3 ADMIRE-CD trial with a 1-year follow-up showed. A total of 212 patients with CD who had been diagnosed for at least 6 months were included. At study enrolment, they had no or only mildly active luminal disease and complex perianal fistulas with two or fewer internal openings and three or fewer external openings. Patients were randomised to a single application of Cx601 or to placebo plus standard of care. The rate of combined remission was significantly better with Cx601 than with placebo (56.3% vs 38.6; P=0.010). In the subgroup of patients who achieved combined remission at 24 weeks, more patients in the Cx601 group than in the placebo group were relapse-free at week 52 (75.0% vs 55.9%; P=0.052). There were no significant between-group differences in clinical remission at week 24, but by week 52, more patients in the Cx601 group than in the placebo group had achieved clinical remission (59.2% vs 41.6%; P=0.013). The rates of TEAEs of any kind were slightly higher in the Cx601 group than in the placebo group (76.7% vs 72.5%; Table 6) [18].

Table 6 TEAEs > 2% of patients [18]

Event	Cx601 group (%)	Placebo group (%)
Anal abscess	13.6	7.8
New anal fistula	3.9	< 1.0
Crohn's disease exacerbation	0.0	2.9

Nine patients in each group withdrew because of AEs whereas 7 patients in each group experienced serious drug-related AEs, leading to 6 patients in the Cx601 group and 7 patients in the placebo group to withdraw from the study [18].

Surgery

Preoperative use of vedolizumab

As the preoperative use of vedolizumab has been associated with an increased risk of short-term postoperative infectious complications, this was assessed in a single-center cohort of patients with UC undergoing (procto)colectomy with ileal pouch-anal anastomosis (IPAA).
A total of 170 patients underwent (procto)colectomy of which 46% were female. The median age was 38 years and the median disease duration was 6 years. Of these, 20% received vedolizumab within 14 weeks, 35% received anti-TNF within 8 weeks and 19% received a moderate-to-high dose (≥ 20 mg/day) of prednisone. A further 42% received no therapy at the time of (procto)colectomy. Surgery was laparoscopy-assisted in 77% of patients; pouch construction was performed at first stage in 28% of patients. This was more frequent in patients with dysplasia/cancer (85% vs 13%, P<0.001), and less frequent in patients under vedolizumab (9% vs 32%, P=0.005), anti-TNF (15% vs 35%, P=0.006), or steroids (0% vs 34%, P<0.001). The only independent risk factor for short-term postoperative infections and overall complications (odds ratio (OR) 3.11 [95% CI 1.52-6.40], P=0.002) was pouch construction at first stage (OR 2.40 [95% CI 1.18-4.90], P=0.016). No significant difference could be observed between different treatment categories and development of short-term postoperative complications. The comprehensive complication index (CCI) and postoperative hospitalisation stay were comparable between each treatment category and only elevated in patients undergoing pouch construction at first stage. Thus, in this large single-center cohort of patients with UC undergoing IPAA surgery, perioperative use of vedolizumab was not associated with short-term postoperative (infectious) complications. However, in patients under biological therapy or moderate-to-high dose of steroids pouch construction should be postponed to the second stage of surgery [19].

The LIRIC trail investigated whether laparoscopic ileocecal resection in comparison to infliximab treatment was effective. Although the QoL outcomes at one year were not significantly better with the IBDQ, laparoscopic ileocecal resection can be considered an acceptable alternative for infliximab in patients with thiopurine or steroid refractory recurrent CD of the terminal ileum. A combined Dutch/British study in 143 patients showed that surgery improved the general QoL and was associated with a reduction in costs compared to infliximab induction and maintenance therapy [6].

In PRACTICROHN - an observational study that included patients aged ≥ 18 years-old who underwent CD-related resection with ileocolonic or ileorectal anastomosis – characteristics and management of CD patients who underwent one surgery was compared with those of patients that underwent more than one surgery. A total of 314 patients was analysed, of which 83% was included in the first surgery and 16% referred previous surgeries. The mean age at diagnosis was similar in the first surgery group (FSG) (33 years) vs the second surgery group (SSG). The age at index surgery was 39 years in FSG vs 43 in SSG (P=0.021). More patients in FSG smoked than in SSG (41% vs 34%, P=0.47). Montreal classification in the two groups were similar except for behavior, with higher proportion of patients with B1 in FSG vs SSG (48% vs 28%) and a higher proportion of B2 and B3 in SSG (29% B2 in FSG vs 46% in SSG and 22% B3 in FSG vs 26% in SSG), P=0.027. Regarding treatment, 13% of patients in the FSG received steroids previous to surgery vs 27% of patients in the SSG (P=0.029). There was no difference in immunomodulators and biological treatment previous to surgery between the two groups. After surgery, a higher proportion of patients received prophylactic treatment with immunomodulators in the SSG compared with FSG (P=0.012). No difference in the rate of colonoscopies performed during the first year after surgery was found between the two groups as well as in the findings at the colonoscopies. Hospitalisations and postoperative complications were also similar. There was no difference in clinical recurrence in SSG in patients receiving or not prophylaxis (P=0.5) whereas in FSG clinical recurrence-free survival was greater in patients with prophylactic treatment (P=0.03). These findings confirm that undergoing second surgery is the main factor of poor prognosis in CD patients, according to the researchers [30].

Hyperbaric oxygen therapy for UC patients

It has been shown that hyperbaric oxygen therapy (HBOT) markedly increases tissue oxygen delivery and case series suggest a potential therapeutic benefit in UC. The therapeutic potential of HBOT as an adjunct to steroids for UC patients hospitalised for moderate-severe flares was assessed in a study by Dulai et al. Included were 18 UC patients hospitalised for moderate-severe flares; they were block randomised across 3 sites in a 1:1 fashion to either steroids + daily HBOT (2.4 ATA @ 100% oxygen, 90 minutes, 10 sessions, N=10) or steroids + daily sham hyperbaric air (1.2 ATA @ 21% oxygen, 90 minutes, 10 sessions, N=8). Sham patients were pressurised to 1.34 ATA to mimic pressure changes observed with HBOT and then decompressed to 1.2 ATA for the remainder of the treatment. The primary outcome was the clinical remission rate at study day 5 (partial Mayo score ≤2 with no sub-score >1). Secondary outcomes were: clinical response (reduction in partial Mayo score ≥2, rectal bleeding sub-score of 0–1) and progression to 2nd line therapy (colectomy, anti-TNF therapy, cyclosporine).

The results showed that HBOT patients had a higher median baseline CRP level (81 vs 10, P=0.07) with comparable mean baseline Mayo scores (9.9 vs 10.9, P=0.14). The study met its primary end-point of clinical remission at study day 5 for HBOT vs sham (50% vs 0%, P=0.04). Response to HBOT was observed as early as day 3 (60% vs 13%, P=0.07) and a significantly higher proportion of HBOT patients achieved day 10 response (80% vs 25%, P=0.05) and remission (50% vs 0%, P=0.04) HBOT patients less often required progression to second line therapy (10% vs 63%, P=0.04) or colectomy specifically (0% vs 38%, P=0.07) while hospitalised. There were no AEs. These findings are promising and further randomised trials are needed to confirm these results findings [23].

Pathophysiology, diagnosis and complications

Novel loci in IBD

Most of the 215 risk loci associated with IBD to date were discovered by genotyping arrays and are driven by common variants. Such assays, however, do not adequately capture lower frequency variation. Thus, the role of these variants in IBD pathogenesis is unclear. A large, multi-faceted study explored the genetic architecture of IBD across the entire allele frequency spectrum; this was done by whole-genome sequencing (WGS) 4,280 IBD patients and comparing them to 3,652 population controls. To increase power to detect an association, this was imputed into new and existing GWAS cohorts totaling over 35,000 individuals, using a reference panel augmented with the sequence data from this study. Finally, this data was combined with publicly available summary statistics and meta-analyses in approx. 60,000 individuals were conducted. With regard to rare variants, an excess burden of rare, damaging missense variants in genes previously implicated in IBD was identified. This suggests that rare variants are likely contributors to IBD pathogenesis. However, no such excess burden was confidently detected in any single gene and much larger sample sizes will be required for their identification. When assessing low-frequency variants, analysis of imputed data identified a missense (Asp439Glu) variant in ADCY7 with 0.6% frequency in the general population, which doubles the risk of UC. Although the good power to detect associations of this type, this was the only variant which was detected, which suggests a minimal contribution to disease susceptibility by low-frequency variants. Evaluating common variants, 24 novel risk loci were identified by meta-analysis. This included three risk loci which contain integrin genes (ITGA4, ITGAV, ITGB8). At two of these, as well as at the previously associated ITGAL and ICAM1 loci, strong evidence was found that the IBD risk-increasing variant increases expression of the respective integrin gene in activated monocytes. This hints at a mechanism linking non-coding genetic associations to targets of existing therapeutics. Also, likely causal missense variants in PLCG2 have identified: mutations in which are known to cause a primary immunodeficiency, and SLAMF8, a negative regulator of inflammatory responses. The researchers concluded that these results highlight the continued value of GWAS and their potentially pivotal role in understanding aspects of disease biology trough the integration of genomic and functional datasets in specific cells and contexts. Minimal evidence was found for strong effects from low frequency variants, despite good power, while the effects of rare variants will require larger sample sizes to be more thoroughly investigated [25].

Epigenetic biomarkers

A five marker methylation marker panel can accurately predict UC associated dysplasia and neoplasia in a population of UC patients as data from phase I of the British Enhanced Neoplasia Detection and Cancer Prevention in Chronic Colitis (ENDCaP-C) trial showed. The ENDCaP-C trial is an observational, multicenter test accuracy study, consisting of two phases. phase I aims to measure the accuracy of a panel of markers on a retrospective cohort of patients with UC whereas in phase 2 (a prospective clinical study), the utility of the panel is ascertained. With regard to phase I, patients were identified from retrospective sample collections from patients undergoing colonoscopic surveillance for UC. These were classified as either having neoplasia, defined as any of adenocarcinoma, high-grade or low-grade dysplasia; non-neoplastic, defined as matched normal mucosal biopsies taken downstream from areas of neoplasia or control, defined as normal mucosa from patients either with or without chronic inflammation who had been screened for neoplasia without it being found. DNA from biopsy samples then underwent bisulphite pyrosequencing of a 11 marker gene panel (SFRP1, SFRP2, SRP4, SRP5, WIF1, TUBB6, SOX7, APC1A, APC2, MINT1, RUNX3). Percentage methylation was log transformed and the three groups compared by t-testing and multivariate logistic regression to predict accuracy. In total, 569 blocks from patients undergoing surveillance were retrieved, consisting of 113 neoplastic, 113 non-neoplastic and 343 control blocks. Of the neoplastic samples, 30.9% were adenocarcinoma and 69.0% were dysplastic. All markers had a success rate of > 90% apart from SFRP1, MINT1 and RUNX3 which were not taken forward to further analysis. In univariate analysis, five markers accurately detected both dysplasia (P<0.0001) and neoplasia (P<0.0001): SFRP2, SFRP4, WIF1, APC1A and APC2. A multivariate logistic regression analysis and ROC analysis

demonstrated the model using the five marker panel had excellent diagnostic accuracy (area under the curve (AUC) = 0.87 [95% CI 0.82–0.92] model P<0.0001). This panel is now being taken forward to prospective validation and in enabling enhanced surveillance in phase 2 of the study [26].

IBD and arterial events

A retrospective review of French hospital discharge data from 2008-2013, which covered the entire French population, demonstrated that severe IBD patients are at higher risk for acute arterial events than people in the general population. The highest relative risk was seen in young CD patients. A total of 210,162 patients aged 15 years and older with IBD diagnosis was identified (CD N=97,708; UC N=112,454). Researchers compared the incidence of a first acute arterial event in patients with IBD with the expected incidence in the general French population matched for geographic region, sex, and 5-year age-specific stratum. The incidence rates for acute arterial events were shown to be higher in both CD and UC patients when compared to the general population (Table 7) [27].

Table 7 Acute arterial events during 595,202 person-years of follow-up [27]

Patient Group	Events (N)	Incidence rate (per 1,000 person-years)
IBD	5,554	9.3
CD	2,244	7.8
UC	3,310	10.7

When assessing all IBD patients, the standardised incidence ratio (SIR) for ischemic heart disease (IHD) was 1.17 (P<0.001), for cerebrovascular disease, it was 1.19 (P<.001), and for peripheral artery disease it was 1.27 (P<0.001). Comparing CD patients with the general population, it emerged that the risk for an event was highest in patients < 55 years (SIR, 1.56), followed by those aged 55-74 years (SIR, 1.38), and patients aged 75 years (SIR, 1.13). In UC patients, the risk was higher in those aged 55-74 years (SIR, 1.15) only. The multivariate analysis – adjusted for age at cohort entry, sex, region, year of cohort entry, disease activity prior to cohort entry, and known cardiovascular risk factors – predictors for acute arterial events included male sex, smoking, hypertension, dyslipidemia, diabetes or alcohol use disorder. There was a significant association between disease activity in the 3 months before and after an IBD hospitalisation and the risk for an arterial event in those with CD (hazard ratio [HR], 1.74) and in those with UC (HR 1.87). The SIRs per IBD subtype are summarised in Table 8 [27].

Table 8 SIRs of acute arterial events by IBD subtype [27]

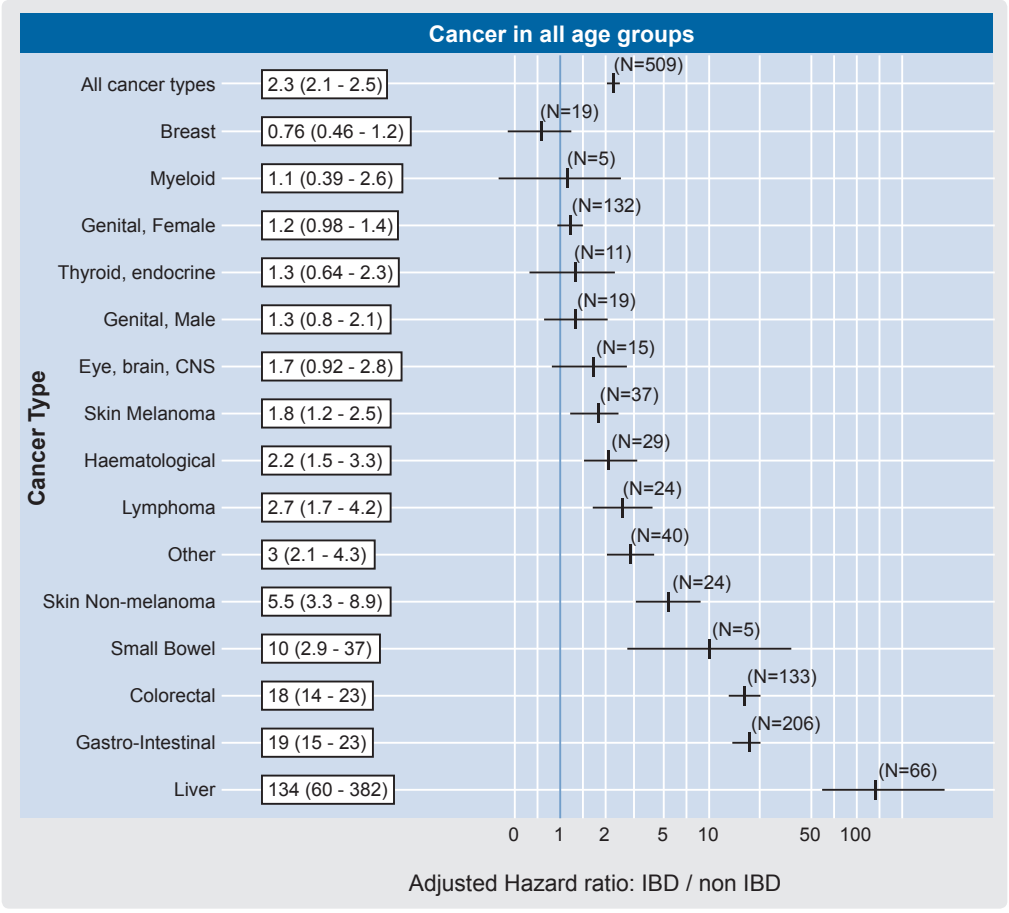
Crohn's disease (287,134 person-years)				
	Reported cases	**Expected cases**	**SIR (95% CI)**	**P-value**
All acute arterial events	2,244	1,658	1.35 (1.30-1.41)	<0.0001
Ischemic heart disease	1,253	956	1.31 (1.24-1.38)	<0.0001
Cerebrovascular disease	694	523	1.33 (1.23-1.43)	<0.0001
Peripheral artery disease	297	180	1.65 (1.46-1.83)	<0.0001
Ulcerative colitis Ulcerative colitis (308,068 person-years)				
	Reported cases	**Expected cases**	**SIR (95% CI)**	**P-value**
All acute arterial events	3,310	3,021	1.10 (1.06-1.13)	<0.0001
Ischemic heart disease	1,924	1,750	1.10 (1.05-1.15)	<0.0001
Cerebrovascular disease	1,021	923	1.11 (1.04-1.17)	<0.01
Peripheral artery disease	365	341	1.07 (0.96-1.18)	0.21

Cancer risk and childhood-onset IBD

Although IBD with onset in adult age has been linked to an increased risk of cancer – especially colorectal cancer (CRC) – risk assessments in childhood-onset IBD are scarce. Swedish researchers investigated this risk by using Cox regression to estimate HRs for cancer in 9,341 individuals with childhood-onset IBD (< 18 years) (UC N=3,380; CD N=3,046; IBD-unclassified (IBD-U) N=2,915) which were compared to 92,224 general population comparators matched for sex, age, year, and place of residence. Data on incident cases of IBD 1964–2014 were obtained from the National Swedish Patient Register comprising both inpatient- and non-primary outpatient care, while cancer data were obtained through the Swedish Cancer Register. Medication data was obtained from the National Prescribed Drug Register for incident cases of childhood onset IBD since 2005 (N=3,386). In total, 509 cases (3.46/1000 person-years) of first cancer in patients with childhood-onset IBD compared to 2,237 (1.52/1000 person-years) in the general population comparators were identified during follow-up. This corresponds to a HR of 2.30 (95% CI 2.09-2.53). HRs for any cancer were 3.19 in UC and 1.76 in CD. Although the relative risk of cancer was highest the first year of follow-up (HR = 6.03), it remained elevated also after ≥ 5 years of follow-up (HR = 2.29; 95% CI 2.07-2.53). Patients who had childhood-onset IBD also had an increased risk of cancer before their 18th birthday (HR = 3.54; 95% CI: 2.22-5.46 N=26 cancers in IBD). GI cancers were associated with the highest relative risks (< 18th birthday: HR = 40, 95% CI 13-175 N=12 cancers in IBD); ≥ 18th birthday: HR = 18, 95% CI 14–23 N=194 cancers in IBD), but the absolute risks were low (Figure 2) [28].

Numbers next to the forest plot represent the number of cancers in IBD-patients, HR (95% CI). Patients who had been exposed to thiopurines (HR = 4.23, 95% CI 2.14-7.91) did not have a significantly more increased risk of cancer than patients who had never been exposed to thiopurines (HR = 3.59, 95% CI 1.5-7.71). These findings clearly show that childhood-onset IBD is associated with an increased risk of cancer, both during childhood and later in life, especially GI cancer. Thiopurine treatment in children is unlikely to be a major risk factor for cancer development in IBD in this age group [28].

Figure 2 HR of cancer in childhood-onset IBD, as compared to matched general population reference individuals 1964–2014 [28]



Numbers next to the forest plot represent the number of cancers in IBD-patients, HR (95% CI).

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